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Exploring the Potential of Biomarkers for Early Diagnosis and Management of Sporadic Creutzfeldt - Jakob disease; A Review

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Abstract

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare and fatal neurodegenerative disorder with no known cure. Early diagnosis of sCJD is crucial for appropriate patient management, but currently, there is no single definitive diagnostic test. However, recent research has shown promising results in identifying novel biomarkers that may aid in the early diagnosis and management of sCJD. This review summarises the current state of biomarker research for sCJD, focusing on the potential of various biomarkers, including cerebrospinal fluid (CSF) biomarkers, neuroimaging techniques, and other potential biomarkers such as blood, urine, and saliva. Using these biomarkers has significantly improved the premortem diagnosis of sCJD, providing patients with valuable information about their condition and enabling them to make necessary plans for the future. Additionally, biomarkers have contributed to our understanding of the disease, paving the way for future therapies and management strategies. While biomarker research for sCJD has shown promising results, there are still several challenges and limitations that need to be addressed. Future research directions include the development of more sensitive and specific biomarkers, the standardisation of diagnostic criteria, and the validation of biomarkers across different patient populations.

Keywords: Biomarkers, Creutzfeldt-Jakob disease, prion disease, sCJD

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Introduction

Sporadic Creutzfeldt-Jakob Disease (sCJD) is a rare and rapidly progressing neurological disorder characterised by the accumulation of abnormal prion protein in the brain (1). It is the most common form of human transmissible spongiform encephalopathies (TSEs) and affects approximately 1 in every 1 million individuals worldwide, with a higher incidence in individuals over 50 (1). The symptoms of sCJD include dementia, muscle stiffness, and involuntary movements, leading to severe disability and death within 1-2 years of onset (2). Despite its devastating impact, sCJD is challenging to diagnose and treat due to limited diagnostic options and effective treatments.

Traditional diagnostic methods for sCJD, such as clinical evaluation, have limited sensitivity and specificity for accurate diagnosis (3). Research has focused on developing biomarkers that can aid in detecting and monitoring sCJD. Cerebrospinal fluid (CSF) biomarkers such as 14-3-3 protein, tau protein, and S100B have shown promise in differentiating sCJD from other neurological disorders with high sensitivity and specificity (4). These biomarkers are present at elevated levels in the CSF of sCJD patients, indicating their potential usefulness as biomarkers. Additionally, other emerging biomarkers such as neurofilament light chain (NfL), prion protein (PrP), and microRNAs (miRNAs) are currently being investigated for their potential in sCJD diagnosis and management.

The development of effective biomarkers has the potential to significantly impact the diagnosis and management of sCJD, ultimately improving patient outcomes. With early detection, physicians can initiate early treatments and interventions to

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slow disease progression and improve patient quality of life. Additionally, biomarkers can aid in monitoring disease progression, enabling physicians to adjust treatment plans accordingly. The purpose of this review article is to explore the potential of biomarkers for early diagnosis and disease progression monitoring in sCJD. Ultimately, the goal of this review article is to inform and inspire further research and innovation in sCJD biomarker discovery and clinical translation.

Methodology

To gather the necessary information, a comprehensive literature search was conducted. Multiple electronic databases, including PubMed, Scopus, Google Scholar and Web of Science, were searched using relevant keywords and Medical Subject Headings (MeSH) terms. The search terms employed were "sporadic Creutzfeldt-Jakob Disease," "biomarkers," "early diagnosis," and "management." The search was restricted to articles published in English up until the date of the literature search. Inclusion criteria were defined to select the appropriate articles for this review. Studies eligible for inclusion explored biomarkers for sporadic CJD in human subjects, with a focus on early diagnosis and/or management. Only studies published in peer-reviewed journals and written in English were considered. Exclusion criteria encompassed studies focusing on genetic or familial forms of CJD, studies lacking sufficient information on biomarkers or early diagnosis/management, non-English studies, and articles published as abstracts, conference proceedings, or editorials without full-text availability.

The screening process involved reviewing titles and abstracts of the initial search results to identify potentially relevant articles. Full-text articles were then assessed for eligibility based on the inclusion and exclusion criteria. Any discrepancies during the selection process were resolved through discussion and consensus among the authors of the review. After this screening process, a total of 55 articles were included for analysis and synthesis. Data extraction was performed for each included study using a standardized form. The extracted information encompassed study characteristics (authors, publication year, study design), participant characteristics, biomarkers investigated, methods used for biomarker detection/assessment, key findings, and implications for early diagnosis and management of sporadic CJD. This data was then synthesized and analyzed to identify common themes, trends, and gaps in the literature.

Biomarkers for sCJD diagnosis and management

sCJD is characterised by a rapid progression of symptoms and a lack of specific clinical or radiological features that can reliably distinguish it from other neurodegenerative diseases (5). Therefore, identifying biomarkers for diagnosing and managing sCJD is critical. Among the biomarkers investigated, protein biomarkers such as 14-3-3 protein and tau protein have been extensively studied due to their ability to reflect the neuronal damage associated with sCJD (5,6). Imaging biomarkers, including magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, have also been investigated for their potential use in sCJD diagnosis and management (7). MRI scans can detect changes in the brain structure and function associated with sCJD, such as cortical ribboning and diffusion restriction. In contrast, PET scans can detect abnormal protein accumulation in the brain. In addition, genetic biomarkers such as PRNP gene mutations have been studied for their potential use in sCJD diagnosis and management (8). These biomarkers can identify individuals at increased risk of developing the disease or who may have inherited the disease-causing mutation from a parent. Identifying and validating biomarkers for sCJD diagnosis and management is crucial for improving the accuracy and speed of diagnosis, as well as the development of effective treatments for this devastating condition.

Cerebrospinal fluid (CSF) biomarkers

CSF biomarkers have emerged as a promising tool for diagnosing and managing sCJD, a disease characterised by the abnormal accumulation of misfolded prion protein leading to neurodegeneration and characteristic clinical features such as rapidly progressive dementia, myoclonus, and ataxia. While a definitive diagnosis of sCJD requires neuropathological examination, CSF biomarkers aid in diagnosing and providing valuable information on disease progression. The most commonly used CSF biomarkers for sCJD are 14-3-3 protein, total tau protein (tau), and neuron-specific enolase (NSE). These biomarkers have demonstrated high sensitivity and specificity in identifying sCJD patients, particularly when combined (9).

A. 14-3-3 protein

14-3-3 protein is a well-studied CSF biomarker for the diagnosis of sCJD. This group of highly conserved acidic proteins is involved in various cellular processes, including signal transduction, cell cycle regulation, and apoptosis (10). In sCJD, the accumulation of misfolded prion proteins in the brain causes neuronal damage and death, releasing 14-3-3 proteins into the CSF (10). The detection and measurement of 14-3-3 protein in the CSF have demonstrated high sensitivity and specificity for sCJD diagnosis (9). However, it is important to note that elevated levels of 14-3-3 protein in the CSF can also be seen in other neurological conditions, such as viral encephalitis, stroke, and brain tumours (11). Therefore, using 14-3-3 protein as a biomarker for sCJD diagnosis should be considered in conjunction with other clinical and laboratory findings. Besides its diagnostic value, 14-3-3 protein provides important information on disease progression and prognosis (12). High levels of 14-3-3 protein in the CSF have been linked to a more rapid disease course and shorter survival time in sCJD patients (12). In 1998, the World Health Organization (WHO) adopted the CSF 14-3-3 diagnostic test for prion disorders (13). The test is typically performed using immunoblotting, but it is not quantitative, and a significant proportion of the results are indeterminate (14). ELISA has been proposed as a quantitative method for determining 14-3-3 levels (14).

Early studies on 14-3-3 protein, such as that of Hsich et al., utilised immunoassays on cerebrospinal fluid mixed with sample buffer and separated by electrophoresis (15). They concluded that the presence of 14-3-3 in cerebrospinal fluid from patients with Creutzfeldt-Jakob disease may be due to massive neuronal disruption and the leakage of brain proteins into the cerebrospinal fluid. They recommended further experiments to determine the quantity and timing of its detection about its clearance in transmissible spongiform encephalopathy.

Huang et al. conducted a study on 46 patients with rapidly progressive dementia. They found that the 14-3-3 protein test in CSF was positive in 82% of cases, with three false-negative and three false-positive results (16). Peckeu et al. reviewed data for 1,572 autopsied patients and found that the diagnostic accuracy of sCJD decreased from 92% to 85% over 18 years, associated with positive detections of 14-3-3 in cases with negative EEG and alternative diagnosis at autopsy (17). Hamlin et al. compared the diagnostic sensitivity and specificity of tau and 14-3-3 protein tests in a large population of patients with prion disease (18). They found that the tau test was less sensitive (87%) but had higher specificity (67/40%) than the 14-3-3 test (90% sensitivity). They noted that the combination of tau and 14-3-3 protein was equivalent to the tau protein test alone. Gerschwind et al. found a lower sensitivity of the 14-3-3 protein in their study, with only 53% of patients with CJD having a positive result (19). Chapman et al. cautioned against over-relying on the 14-3-3 protein as a diagnostic tool based on their experience with three patients with falsely positive or falsely negative results (20). Beaudry et al. compared 14-3-3 protein, neuron-specific enolase (NSE), and S-100 protein as diagnostic markers for CJD in 129 patients (21). They found that S-100 had the highest sensitivity (94.2%), followed by 14-3-3 (89.8%) and NSE (79.7%). They could correctly discriminate between 'CJD' or 'non-CJD' categories in 94.4% of cases using 14-3-3 protein.

B. TAU Protein

Tau is a crucial microtubule-associated protein (MAP) that governs the regulation of microtubules (MT) to ensure proper cytoskeletal organisation and trafficking (22). The physiological functions of tau in modulating MTs, such as polymerisation, stabilisation, and suppression of MT dynamics, are critical. Dysregulation of the tau-MT complex can cause detachment and instability of MTs, which can result in impaired cellular polarity and viability (23).

In tauopathies such as Alzheimer's disease and frontotemporal lobar degeneration, misfolded and aggregated forms of tau protein accumulate in the brain, a neuropathological hallmark (24). Tau aggregates can propagate tau pathology, prion-likely erring from one cell to another and causing misfolding and aggregation of healthy tau molecules in previously healthy cells (25). The mechanisms involved in the cell-to-cell transfer of tau aggregates are diverse, partially understood, and not mutually exclusive. Extracellular tau can exist in various forms, including as a free protein and vesicles, and can be internalised by neighbouring cells via endocytic, pinocytic, and phagocytic mechanisms. Prion-like propagation of misfolded protein pathology could provide a general mechanism for disease progression in tauopathies and other related neurodegenerative diseases (26).

Cseh and colleagues conducted a preliminary retrospective analysis on the usefulness of measuring total Tau (tTau) and other biomarkers from cerebrospinal fluid (CSF) in the diagnostic workup of Creutzfeldt-Jakob disease (CJD) in patients with rapidly progressive dementia (27). The study reported 100% sensitivity for 14-3-3 but only 40% specificity to support the clinical diagnosis of CJD. The sensitivity values were calculated to be 100% or 83%, while the specificity values were 71% or 86%, depending on the applied cut-off levels. The authors noted that the poor specificity of 14-3-3 is not consistent with literature data and could be the result of the small number of patients in the cohort with non-prion disease. Combining these and novel chemical biomarkers may enhance sensitivity and specificity to a desired level.

Kovacs et al. investigated phospho-Tau (pTau) immunoreactivities in 75 sporadic Creutzfeldt-Jakob disease (CJD) cases, examining the entorhinal cortex and six hippocampal subregions (28). Among the cases, 12 (16%) presented only small tau-immunoreactive neuritic profiles, while 52 (69.3%) showed additional tau pathology in the medial temporal lobe consistent with primary age-related tauopathy (PART). Additionally, 11 cases (14.7%) demonstrated widespread tau pathologies compatible with primary tauopathies or the gray matter type of ageing-related tau astrogliopathy (ARTAG). Analysis of cerebrospinal fluid revealed a significant increase in total tau protein in cases with widespread tau pathology, while pTau (T181) level was only elevated in four cases. The frequency of tau pathologies was not unusually high in sporadic CJD, and it was not related to PrP deposition. The authors concluded that the current examination of cerebrospinal fluid pTau (T181) level does not reliably reflect primary tauopathies, PART, and ARTAG seen in brains with CJD.

Rubenstein et al. investigated the usefulness of the Tau protein in the blood for identifying and classifying prion-related disorders, comparing samples from sCJD in humans and three well-studied mouse-adapted scrapie strains (29). They distinguished between two subtypes of Tau protein, T-Tau and P-Tau. They argued that the loss of Tau's normal function of stabilising microtubules leads to a pathological disturbance in the cytoskeleton's normal structure, causing synaptic dysfunction. The authors found that T-Tau, but not P-Tau, was significantly elevated in clinical sCJD cases compared to normal controls in both the human brain and plasma samples. Measuring T-Tau and P-Tau and calculating the P-Tau/T-Tau ratio from prion disease blood samples may be useful for discriminating patients with CJD from individuals with other neurodegenerative disorders. The authors suggested that the role of Tau phosphorylation in human prion diseases initiated by infection (iCJD) may be significant and in contrast with its role in human prion diseases where an infectious source is yet to be identified (sCJD).

Otto et al. analysed the cerebrospinal fluid (CSF) of 297 patients with a differential diagnosis of CJD, 23 non-demented

control subjects, and 15 non-CJD patients with positive 14-3-3 immunoblots to determine the sensitivity and specificity of Tau protein (30). Their results indicated a diagnostic sensitivity of 94%, a specificity of 90%, and a positive predictive value of 92% for tau-protein at a cut-off of 1,300 pg/mL. The authors concluded that for patients with type II prion protein and methionine/valine or valine/valine polymorphism at codon 129, tau-protein has a higher diagnostic sensitivity than 14-3-3 protein.

Similarly, Wang et al. analysed 202 CSF samples from clinically suspected patients with sporadic CJD for tau protein and signal transduction regulatory protein 14-3-3 protein (31). The authors found increased levels of tau protein and an increased incidence of 14-3-3 positivity in probable CJD cases, with a threshold of 1400 pg/mL. The combination of raised tau and positive 14-3-3 increased the specificity but slightly reduced the sensitivity. Statistical analysis indicated that the raised level of tau positively correlated with the presence of 14-3-3 in CSF.

C. Real-Time Quaking Induced Conversion (RT-QuIC)

Real-Time Quaking Induced Conversion (RT-QuIC) is an emerging biomarker with great potential for detecting prion diseases, including sCJD. RT-QuIC is an extremely sensitive and specific technique capable of detecting even trace amounts of the abnormal prion protein in biological fluids such as CSF or blood of individuals with prion diseases (32). The methodology of RT-QuIC involves mixing a small volume of the patient's biological fluid with a substrate containing recombinant prion protein, followed by agitation and real-time monitoring of amyloid fibril formation via fluorescence or turbidity changes (33). The amplification of the fibril formation detects the presence of the abnormal prion protein in the patient's fluid. Compared to conventional methods for detecting prion diseases, RT-QuIC has several advantages. It is quicker, more sensitive, and more specific than the Western blot method, considered the gold standard (32). Moreover, RT-QuIC can detect prion diseases early, even before clinical symptoms appear, and can differentiate between different prion diseases (34).

Multiple studies have validated the diagnostic accuracy of RT-QuIC for prion diseases, demonstrating its significant potential as a tool for diagnosing and managing prion diseases, including CJD. However, further research is still necessary to standardise and optimise the technique's sensitivity and specificity in clinical practice. Atarashi et al. studied Japanese and Australian subjects, which yielded sensitivity and specificity rates greater than 80% and 100%, respectively (35). Meanwhile, Rhoads et al. analysed over 10,000 cerebrospinal fluid (CSF) specimens and found that RT-QuIC had high diagnostic sensitivity and specificity across all prion diseases (36). However, its diagnostic accuracy was lower for certain prion diseases, such as fatal familial and sporadic fatal insomnia. The authors also observed that younger individuals with prion disease and negative RT-QuIC results had lower tau and non-elevated 14-3-3 levels than RT-QuIC-positive cases. In a separate study, McGuire et al. analysed 108 CSF samples from patients with confirmed sCJD and control patients (37). The exploratory study showed that RT-QuIC had a sensitivity of 91% and a specificity of 98% for diagnosing sCJD. The confirmatory study revealed a sensitivity and specificity of 87% and 100%, respectively. These findings suggest that CSF RT-QuIC analysis can potentially be a more specific diagnostic tool for sCJD than current CSF tests.

D. Neurofilament Light Chain

Neurofilament light chain (NfL) is a biomarker studied in the context of sCJD (38). Studies have shown that levels of NfL are elevated in the cerebrospinal fluid (CSF) and blood of patients with sCJD compared to healthy individuals (38,39). This elevation is thought to reflect the degeneration and loss of neurons in the brain, a hallmark of sCJD. In addition, NfL levels in CSF have been shown to correlate with disease progression and severity in sCJD (40). Patients with more advanced sCJD have higher levels of NfL in their CSF, indicating a greater degree of neuronal damage.

The use of NfL as a biomarker for sCJD has several potential advantages. It is a non-invasive and easily accessible marker that can be measured in CSF or blood samples (40). It has also shown promise as a tool for monitoring disease progression and response to treatment in other neurodegenerative diseases, such as Alzheimer's and multiple sclerosis.

In a study by Zanusso et al., the authors investigated the potential use of NfL as a biomarker for sCJD (41). They analysed CSF samples from 49 patients with sCJD, 21 patients with other neurological diseases, and 19 healthy controls. They found that NfL levels were significantly elevated in sCJD patients compared to healthy controls and patients with other neurological diseases. The median NfL level in sCJD patients was 2,044 pg/mL, compared to 320 pg/mL in healthy controls and 729 pg/mL in patients with other neurological diseases. Furthermore, the study found that NfL levels were correlated with disease severity and survival time in sCJD patients. The authors noted that NfL levels were significantly higher in patients with rapidly progressive disease and shorter survival times. This suggests that NfL could be a prognostic marker in sCJD, providing important information about disease progression and potential treatment options. The study by Zanusso et al. provides promising evidence for using NfL as a biomarker for sCJD. However, further research is needed to validate these findings in larger patient cohorts and to determine the optimal methods for measuring NfL levels in both CSF and blood samples.

In a study by Van Ejik et al., cerebrospinal fluid (CSF) levels of neurofilament light (NFL) and heavy chain (NFHp35), total tau (t-tau), and glial fibrillary acidic protein (GFAP) were examined to differentiate between sporadic Creutzfeldt-Jakob disease (sCJD) and Alzheimer's disease (AD) (42). Their results revealed significantly increased median levels of NFL, NFHp35, GFAP, and t-tau in sCJD patients compared to AD patients, suggesting greater neuroaxonal damage in sCJD. Although GFAP concentrations did not differ between sCJD and AD, these findings highlight the potential of NFL and

NFHp35 as diagnostic tools for rapidly progressive dementias. However, prospective studies are needed to validate their clinical utility.

Similarly, in a study by Zerr et al., CSF NFL levels were measured in various neurodegenerative and non-neurodegenerative conditions (43). The highest levels of NFL were found in sCJD, followed by AD, dementia with Lewy bodies/Parkinson's disease dementia, frontotemporal dementia, vascular dementia, and mild cognitive impairment. The study demonstrated that NFL levels could differentiate sCJD from non-neurodegenerative neurological and psychiatric conditions, as well as from other diagnostic groups exhibiting cognitive decline or dementia not caused by CJD. These findings suggest that NFL levels could be a useful diagnostic biomarker for sCJD.

Imaging biomarkers

Advanced imaging techniques have transformed the diagnosis and monitoring of sCJD. Magnetic resonance imaging (MRI) detects characteristic changes in brain tissue and monitors disease progression. Positron emission tomography (PET) identifies alterations in brain metabolism, aiding disease diagnosis and monitoring. Single-photon emission computed tomography (SPECT) and electroencephalography (EEG) have also shown promise in detecting changes in cerebral blood flow and abnormal electrical patterns, respectively. The use of these imaging techniques improves diagnostic accuracy and enables early identification and better treatment options for sCJD patients.

A. Magnetic resonance imaging (MRI)

MRI is a noninvasive imaging modality that employs a strong magnetic field and radio waves to generate high-resolution brain images (44). In sCJD, MRI is an essential tool for detecting characteristic changes in brain tissue. These changes manifest as hyperintense signals in the basal ganglia and cerebral cortex. Additionally, MRI can detect atrophy in the same brain areas (45).

During the early stages of sCJD, MRI may show only mild changes or even be entirely normal. However, as the disease progresses, characteristic changes become more evident. The appearance of hyperintense signals in the basal ganglia and cerebral cortex is a specific finding in sCJD and is often used to differentiate it from other neurodegenerative disorders (46). One advantage of MRI is that it is non-invasive and does not involve ionising radiation. This makes it a safer alternative to other imaging modalities, such as computed tomography (CT), which uses ionising radiation to generate brain images. MRI is also a versatile imaging technique, allowing for using different pulse sequences to highlight specific features of brain tissue.

In a study by Sakai et al., 11 patients with dCJD who were methionine homozygous at codon 129 of the prion protein gene underwent DW-MRI scans (47). In non-plaque cases, brighter hyperintensity was observed in the cerebral cortex and basal ganglia on the side of dural grafting. Later DW-MRI revealed extensive hyperintense lesions in the brain. In plaque-type cases, initial scans showed hyperintensity in one patient's thalamus and basal ganglia. A thalamic-specific hyperintensity was observed in the third patient after seven months of treatment. These findings suggest that different prion strains propagate in non-plaque and plaque types with different patterns.

Bizzi et al. utilised two data-driven methods for subtype detection in 1,458 patients with MRI (48). The procedure-prion subtype classification algorithm with MRI (PriSCA_MRI) correctly diagnosed the three most common subtypes with 82% accuracy, while the addition of Gen increased accuracy to 89% and correctly identified every subtype. The sensitivities for diagnosing the two most frequent sCJD subtypes, MM1 and VV2, were up to 95% and 97%, respectively. The algorithms provide the first usable antemortem sCJD subtype diagnosis.

In another study by Lodi et al., 29 patients were enrolled based on clinical and electroencephalographic features, excluding the results of CSF 14-3-3 determination for initial diagnosis (49). The accuracy of magnetic resonance modalities such as 1H-MRS, diffusion-weighted imaging, and FLAIR-T2 in diagnosing prion disease was evaluated. Fourteen out of 29 patients were diagnosed with prion disease, with diffusion-weighted imaging showing an 86% accuracy rate. At the same time, NAA/Cr, NAA/myoinositol, and CSF 14-3-3 protein had an accuracy rate of 86%, 90%, and 86%, respectively.

B. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)

[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is an increasingly utilised non-invasive imaging technique for evaluating patients suspected of sCJD. It measures the cerebral metabolic rate of glucose (CMRglc) and offers regional glucose utilisation information in the brain (50). Studies indicate FDG-PET is a useful tool for sCJD diagnosis and differential diagnosis. FDG-PET differentiates sCJD from other neurodegenerative diseases with similar clinical features (50,51). Ortega-Cubero et al. reported FDG-PET distinguishes between sCJD and Alzheimer's disease, with sCJD patients displaying a cortical hypometabolism pattern distinct from Alzheimer's disease (52). FDG-PET is a valuable tool for sCJD diagnosis, differential diagnosis, and monitoring. Its regional glucose utilisation information in the brain has the potential to improve diagnostic accuracy and distinguish sCJD from other neurodegenerative diseases.

Renard et al. investigated the use of [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) as an imaging marker in sCJD (53). The study evaluated the relationship between clinical pattern and cerebral glucose metabolism in consecutive CJD patients, assessing predefined clinical signs such as ataxia, visual, pyramidal, myoclonus, limb apraxia, limb dystonia, sensory, parkinsonism, and corticobasal syndrome (CBS) along with FDG-PET data. Statistical parametric mapping (SPM) analyses were performed to compare patients with and without specific clinical signs and CJD patients with healthy controls. The

study found that 15 CJD patients exhibited lateralised frontal and parietal hypometabolism, indicating the potential use of FDG-PET as an imaging marker in CJD. Among the patients, 11 were probable, and two were histologically proven sporadic and genetic CJD, respectively.

Other potential biomarkers

Other potential biomarkers, such as blood, urine, and saliva, have also been investigated for their potential use in diagnosing and monitoring sCJD. One potential biomarker is the prion protein, which can be detected in blood (54). However, the sensitivity and specificity of this method are currently not high enough for clinical use. Other blood-based biomarkers investigated include total tau protein, which is elevated in sCJD patients, and S100B, which is released into the bloodstream in response to brain injury. However, the clinical utility of these biomarkers remains to be established. Urine and saliva have also been investigated as potential sources of biomarkers for sCJD. Urine testing for the presence of the prion protein has been investigated, but its sensitivity and specificity are currently limited.

State of knowledge on the use of biomarkers for sCJD

The use of biomarkers in diagnosing and managing sCJD has been a topic of interest in recent years. Biomarkers are measurable indicators of biological processes that can provide valuable information about the presence, severity, and progression of a disease (55). In the context of sCJD, biomarkers have the potential to aid in early and accurate diagnosis, monitoring disease progression, and evaluating treatment efficacy. However, there are also potential drawbacks and limitations to using biomarkers in sCJD.

One of the most significant benefits of using biomarkers in sCJD is the potential for early and accurate diagnosis. Before using biomarkers, diagnosis of sCJD relied on clinical symptoms and the exclusion of other conditions that may have similar symptoms. This process was time-consuming, expensive, and often inconclusive. The use of biomarkers, such as the presence of 14-3-3 protein in CSF or abnormal prion protein in brain tissue, aid in diagnosing sCJD with higher sensitivity and specificity, allowing for earlier detection and more accurate diagnosis. This can lead to earlier interventions and improved patient outcomes.

Another potential benefit of using biomarkers in sCJD is the ability to monitor disease progression and evaluate treatment efficacy. Biomarkers provide information about the severity and progression of the disease, as well as the effectiveness of treatments. This can aid in developing personalised treatment plans, allowing for more targeted and effective therapies. Additionally, biomarkers can help identify individuals at increased risk for developing sCJD, allowing for early intervention and prevention strategies.

However, there are also potential drawbacks and limitations to using biomarkers in sCJD. One limitation is the lack of standardisation and validation of biomarker assays. There is currently no consensus on which biomarkers are most useful or reliable for diagnosing and managing sCJD, and the interpretation of biomarker results can vary between laboratories. This can lead to inconsistencies in diagnosis and treatment and may limit the usefulness of biomarkers in sCJD.

Another potential limitation is the invasiveness of some biomarker tests. For example, collecting CSF for detecting 14-3-3 protein requires a lumbar puncture, which can be uncomfortable and carries a small risk of complications. Similarly, detecting abnormal prion protein in brain tissue requires a biopsy or post-mortem examination, which may not be feasible or desirable for all patients. These limitations restrict the use of biomarkers in some populations and may limit the utility of biomarkers for disease monitoring and evaluation.

Additionally, biomarkers may not be specific to sCJD and may also be present in other neurodegenerative diseases. For example, elevated levels of NfL have been observed in other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, as well as in traumatic brain injury (10). This can lead to false positives and may limit the usefulness of biomarkers for diagnosing and managing sCJD.

The use of biomarkers in sCJD raises ethical and psychological concerns. Detecting a biomarker for sCJD may lead to anxiety and distress for patients and their families, particularly if there is no effective treatment or cure. Additionally, using biomarkers for disease prediction may lead to stigmatisation and discrimination for individuals at increased risk for developing sCJD.

Current biomarker research faces several challenges and limitations in the context of sCJD. One challenge is the limited understanding of the underlying pathophysiological mechanisms of the disease, which can hinder the identification of reliable biomarkers. sCJD is a complex neurodegenerative disease with various clinical and neuropathological presentations, and researchers have yet to fully elucidate the mechanisms that contribute to its development and progression. Another challenge is the heterogeneity of sCJD, which can make it difficult to identify biomarkers that accurately reflect disease status. There are different subtypes of sCJD, each with distinct clinical and pathological features, and these subtypes may respond differently to potential treatments. Therefore, biomarkers may need to be subtype-specific to reflect disease status and predict treatment response accurately.

Additionally, the limited availability of well-characterized patient samples can be a major limitation in biomarker research for sCJD. Due to the rarity of the disease, obtaining large and diverse patient cohorts can be challenging, limiting the statistical power and generalizability of biomarker studies. Moreover, the high cost and complexity of some biomarker assays can also be a challenge in sCJD research. Many biomarker assays require specialised equipment and expertise, and this can limit their availability and accessibility to researchers and clinicians, particularly in resource-limited settings.

Future research directions for improving biomarkers for sCJD

In the future, research on biomarkers for sCJD should focus on improving the sensitivity and specificity of existing markers and identifying new biomarkers specific to the disease. One promising avenue for research is using advanced imaging techniques, such as PET and SPECT, to detect changes based on changes with sCJD. These techniques may provide a more accurate and earlier diagnosis of the disease. Another potential area of research is identifying genetic and epigenetic factors associated with sCJD. By identifying specific genetic and epigenetic markers associated with sCJD, researchers may be able to develop more targeted and effective therapies for the disease. In addition, the use of machine learning and artificial intelligence (AI) may also help to improve the accuracy of sCJD diagnosis and prognosis. By analysing large datasets of clinical and biomarker data, these tools may identify patterns and correlations that are not immediately apparent to human observers. Finally, further research is needed to understand better the underlying mechanisms of sCJD and the role that biomarkers play in the disease. By elucidating the biological processes involved in sCJD, researchers may be able to develop more effective treatments for the disease.

Conclusion

The investigation of novel biomarkers for early diagnosis and management of sCJD has shown significant progress in recent years. This neurodegenerative disease is a challenging condition, and the lack of effective diagnostic tools has been a major barrier to providing appropriate care for patients. However, the identification of several promising biomarkers, including 14-3-3 protein, tau protein, and NfL, has provided a new avenue for the development of pre-mortem diagnostic tests and monitoring tools.

Despite these promising developments, there are still significant challenges and limitations in the field of biomarker research for sCJD. The rarity and heterogeneity of the disease, as well as the lack of reliable animal models, have hindered the identification and validation of potential biomarkers. Additionally, the specificity and sensitivity of current biomarkers need to be further evaluated and optimised to improve diagnostic accuracy.

Future research in the field of sCJD biomarkers should focus on developing more reliable and specific tests that can accurately diagnose the disease at an early stage. The exploration of other potential biomarkers, such as miRNAs, exosomes, and prion seeding activity, may provide valuable insights for the development of new diagnostic and therapeutic strategies. Additionally, more extensive longitudinal studies that involve larger patient cohorts and include both clinical and neuropathological data are required to improve our understanding of the disease and validate the use of biomarkers in clinical practice.

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Ethical approval

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Availability of data and material

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Consent for publication

This manuscript has been approved for publication by all authors.

Author Contribution

Conceptualization was done by NA. Writing of first and final manuscript was done by all authors.

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