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Neuropsychiatric Symptoms among the Major Categories of Creutzfeldt-Jakob Disease

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Abstract Creutzfeldt-Jakob disease (CJD) is a progressive terminal neurodegenerative disease classified within the human prion disorders. There are four distinct categories of the disorder: variant, iatrogenic, sporadic and familial. Onset is typically precipitous with death occurring within a year of symptom commencement. Worldwide incidence is approximately one case per million per population each year. In the United States this translates to roughly 300 new cases a year. Presentation typically occurs between 50 and 70 years of age with median age onset of 60 and is without gender bias. Currently, no cure exists and treatment is only palliative for symptoms. Classic features of CJD include rapidly progressive dementia, myoclonus and ataxia, yet most case reports have demonstrated initial presentation in the form of nonspecific psychiatric and neurological symptoms. Since wide-ranging psychiatric symptoms are frequently the first indices of the disease, this paper reviews the symptoms across the four categories of CJD. Misdiagnosis early in the course of the disease is problematic and occurs most frequently from symptom heterogeneity. The preponderance of evidence suggests that since initial symptoms can occur with or without the hallmark signs of the disease, utilization of a global approach for early detection and diagnosis is warranted that is inclusive of repeated, supportive diagnostic tests performed at various points in time. Consideration of the patient and family and the benefits of obtaining an early diagnosis as it relates to the provision of care, treatment, and support are discussed in light of these findings.

Keywords Creutzfeldt-Jakob disease (CJD), Prion, Mad cow disease, Spongiform encephalopathy

1. Introduction

Alfons Jakob first defined what is known today as Creutzfeldt-Jakob disease (CJD) in 1921 with reference to Hans-Gerhard Creutzfeldt's similar work in 1913 [1]. Although a rare disease, CJD is unique in that it is a prion (proteinaceous infectious particle) disease. Prion diseases are a set of communicable, progressive, and ultimately fatal neurodegenerative disorders where an aberrant folding of a host-encoded prion protein (PrP) occurs in abundance [2]. Prion diseases occur in both humans and animals [3]. The disease affects the central nervous system (CNS) and is classified as a transmissible spongiform encephalopathy (TSE) [4, 5]. This group of diseases became a household name in the 1980s when "mad cow disease" or bovine spongiform encephalopathy epidemic ensued in the United Kingdom from contaminated cattle feed that infected cattle stock and then ultimately infected consumers [3].

There are four main categories of CJD: familial CJD (fCJD) – which is inherited and occurs in 15% of CJD cases; variant or new-variant CJD (vCJD or nvCJD) – which is transmissible from animal to human through bovine spongiform encephalopathy (BSE or "mad-cow" disease) contamination; iatrogenic CJD – which is transmissible from human to human through medical procedures; and sporadic (sCJD) – which does not have any of the previous described causes and accounts for 85% of all CJD cases [4, 6]. According to Chao and Han [7], since initial clinical manifestations of CJD patients are often non-specific and diverse, the diagnosis of the disease can be problematic. Additionally, the potential exists for physicians from numerous disciplines to have initial contact in caring for these patients, as the clinical presentation may be exhibited through behavior, sensory, motor, or cognitive dysfunctions, which therefore increases the probability for misdiagnosis [7]. Since wide-ranging psychiatric symptoms are frequently the first indications of the disease, it is important to know what they are and if they vary across the different categories of CJD [6, 8]. The purpose of this paper is to define the symptoms across the different classifications of CJD.

In addition to preventing further spread of the disease iatrogenically, early recognition and diagnosis can provide more successful symptom treatments that can ease the stress of the disease on the patient and caregiver. Furthermore, because to date there is no cure or treatment to prolong

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survival, and because of the rapidity and fatal trajectory of the disease, early detection and diagnosis can afford the patient and their family to be able to make palliative care and end of life decisions while the patient is still cogent. Last, early recognition of the disease and the point in time that the disease is correctly diagnosed can have marked significance especially if treatment modalities do become available that can be rendered to the patient [9].

2. Brief History of CJD

The first account of human spongiform encephalopathies commenced in the early 20th century. In 1920, Breslau neurologist Hans Gerhard Creutzfeldt described a case of a 22 year-old female with a clinical presentation of advanced terminal degenerative dementia accompanied by numerous neurological anomalies that included both myoclonus and spasticity [10]. Shortly thereafter, Hamburg neuropathologist Alfons Maria Jakob published a manuscript detailing the clinical presentation of two men and three women between the ages of 34 and 51 who demonstrated progressive motor function, alterations in speech, emotion, personality, and memory loss [11]. More serious symptoms rapidly ensued, such as the inability to stand, move or speak, and all five patients succumbed within a year after the initial onset of symptoms [11, 12]. The name Creutzeldt-Jakob disease arose then, after Jakob concluded that Creutzfeldt's single case study paralleled his own cases in both presentation and outcome [12]. Later, the term subacute spongiform encephalopathy was suggested, with spongiform change in the CNS now recognized as the hallmark definitive diagnostic criterion for the disease [13]. Interestingly, after a retrospective review of the initial case reports years later, it was discovered that the first cases documented by Creutzfeldt in 1921, did not actually meet the required histological benchmarks for the disease [13]. On the contrary, two of Jakob's cases did demonstrate the histological spongiform change in the CNS. Yet to this day, Creutzfeldt-Jackob disease has remained the accepted medical nomenclature for the disorder [14]. However, Katscher [12] writes that to give "historical justice" to Jakob and to accredit him with first discovering the disease, the name order is commonly reversed to Jakob-Creutzfeldt disease within the German medical literature (p. 11).

3. Incidence and Prevalence

The Creutzfeldt-Jakob Foundation [3] reports the incidence of CJD worldwide is about one case per million per population each year. In the United States this translates to about 300 cases a year. CJD shows no gender bias and in sCJD, presentation usually occurs within the fifth and seventh decade of life, with a median onset occurring in the sixth decade [8]. For the iatrogenic form (iCJD), the age of onset depends on the age at time of the exposure as well as the incubation time and in vCJD there is a younger onset with longer duration than the sporadic form [3]. In fCJD, there is oftentimes a younger age of onset than sCJD, with occurrence resulting from either a stressor or sporadically as in the other categories, but the course after onset is similar to sCJD [15, 16].

4. Diagnosis

The classic features of CJD consists of a triad of symptoms that include dementia, myoclonus, and ataxia, yet initial clinical portraiture via case reports in the extant literature have demonstrated initial presentation in the form of nonspecific psychiatric and neurological symptoms [7, 8, 17-20]. Aside from a clinical assessment of the patient (complete history and physical exam), supportive tests for probable diagnosis may be administered and include magnetic resonance imaging (MRI), electroencephalography (EEG) and lumbar puncture [3]. The cerebrospinal fluid (CSF) obtained from the lumbar puncture is tested with an immunoassay 14-3-3 test that looks for the presence of 14-3-3 protein in the CSF [2, 3, 21]. This protein is released into the CSF indicating an extensive destruction of neurons [3], one criterion of probable CJD [21]. However, it should be noted other brain disorders can yield a positive assay result and therefore probable diagnosis requires additional criteria that need to be met [21]. The World Health Organization (WHO) [22] outlines these additional criteria.

The WHO criteria [22] for probable diagnosis of sCJD are as follows: (1) exclusion of alternative diagnoses with routine investigations; (2) rapid progressive dementia; (3) at least two of the following four clinical features-myoclonus, visual disturbance or cerebellar dysfunction, pyramidal, or extrapyramidal feature, and akinetic mutism; (4) a typical EEG pattern (periodic sharp-wave complex), and/or CSF positive for 14-3-3 by immunoblot; and (5) a clinical duration of less than 2 years before death. Interestingly, the WHO does not include MRI as diagnostic criteria for probable sCJD, although the University of California, San Francisco has updated guidelines that support the utilization of the MRI as an adjunctive criterion for diagnosis of the disorder [23]. Definitive diagnosis for CJD is only positively confirmed through pathological inspection of brain tissue post-mortem [3].

4.1. Variant CJD (vCJD)

Spencer et al. [24] retrospectively examined the first 100 cases of vCJD recorded in the United Kingdom for predominant psychiatric symptoms. The researchers felt the widespread occurrence of the variant made an analysis of the early diagnostic features important for establishing diagnostic criteria. Every neurological and psychiatric symptom was recorded and then clinically similar features were clustered together. In the cases reviewed, psychiatric symptoms presented almost immediately about 85% of the time. Comparatively, neurological symptoms occurred in about 40% of the cases from the start. On average, the first

psychiatric symptom occurred at zero months, and the first neurological symptoms occurred at two months from onset. At less than four months, common psychiatric symptoms included depression, withdrawal, anxiety, irritability, insomnia, and loss of interest. Less common were behavioral changes, anergia, and poor performance. Obsessive features, losing things, panic attacks, and suicidal ideation were rarely noted. There were no common neurological symptoms at this stage, and pain was the only less common symptom. Rarely, headaches, dropped items, sweatiness, and loss of consciousness were recorded. Between 4 and 6 months, poor memory, impaired concentration, and aggression were common. Less common were tearfulness, weight loss, appetite change, hypersomnia, and confusion. Rarely psychomotor retardation, diurnal mood variations, and loss of confidence occurred. Neurologically, gait disturbances and slurring of speech were common, and unexplained skin sensations or numbness were less common. Rarely, tremors, impaired handwriting, coldness, odd sensations, dizziness, and cranial motor weakness were noted. After 6 months from onset, disorientation and agitation were the only common psychiatric symptoms noted. Less common were hallucinations, impaired self care, paranoid delusions, and inappropriate affect. Rarely, bizarre behavior, paranoid ideation, recognition impairment, confabulation, lack of emotion, perseveration, impaired comprehension, change in eating preferences, impaired use of devices, and acalculia were recorded. At this time neurologically, hyperreflexia, impaired coordination, myoclonus, incontinence, and eye features were common. Chorea, extensor plantar responses, impaired swallowing, clonus, hypertonia, and primitive reflexes occurred less commonly. Rarely, the following neurological symptoms were noted: dysdiadochokinesia, taste disturbances, startle response, hypersensitivity, peripheral motor weakness, and sound sensitivity. The researchers concluded that patients presenting with a combination of a psychiatric disorder with psychotic or affective features and dysarthria, persistent pain, gait ataxia, or sensory symptoms should trigger a suspicion of vCJD. The problems with this study were that the onset of the disease was determined by the recorded data. Psychiatric or neurological symptoms could have been present but not recorded prior to the time it was noted. Also, late features, such as bed boundness or muteness, were not included because the information was deemed less reliable. However, this study on vCJD enabled others to search for evidence of the neuropsychiatric symptoms that presented early in the progression of other categories of CJD.

4.2. Sporadic CJD (sCJD)

Wall et al. [5] analyzed sCJD in 126 case studies from the Mayo Clinic to see if psychiatric symptoms were present prior to diagnosis with the disease. Since vCJD was associated with psychiatric symptoms, the study examined if similar symptoms were noted in the sCJD variant. All psychiatric symptoms that were noted in the case files reviewed in this study occurred within the first 100 days of the onset of the illness. Most frequently, sleep disturbances were noted among patients and included: insomnia, hypersomnolence, and mixed or other sleep disturbances. Psychotic symptoms such as delusions, paranoia, confabulation, and perseverations that involve disorganized speech, behavior, and thought processes, as well as frequently recorded visual and auditory hallucinations. Rarely, psychotic symptoms such as tactile and olfactory hallucinations, dissociation, and catatonia were experienced. Less frequently, but still significantly, 49 patients had recorded depressive symptoms. Of these, the most prevalent were weight loss, sad or depressed affect, withdrawn behaviors, and personality changes. However, fatigue, hospitalization for depression, decreased appetite, increased tearfulness, anhedonia, apathy, increased guilt and decreased libido were also present. Agitation and behavioral dyscontrol occurred with agitation and violent/ belligerent/ combative behaviors appeared most frequently and irritability, bizarre behaviors, irrational anger, emotional lability, and confusion or wandering were noted less commonly. Anxiety symptoms were also remarked upon and included anxious, worried, and nervous affect. Additionally, subjective reports recorded were panic attacks, restlessness, and non-myoclonus tremors which appeared less frequently. Other psychiatric manifestations rarely reported were conversion disorder, obsessive and repetitive behaviors, somatoform illness, and personality change not otherwise specified. In all cases, most psychotropic treatments had a predominantly neutral effect. However, anxiolytic, hypnotic, and antipsychotic treatments showed significant positive results as well. The researchers concluded that sCJD should be included in the differential diagnosis of patients presenting with new onset dementia, especially if it is associated with sleep problems, psychosis, or symptoms of depression that continue or worsen even with standard treatment. It was also suggested that neuropsychiatric treatments could improve the quality of life for both caregivers and patients. One of the problems with this study was that it only reviewed medical records. No objective neuropsychiatric assessments were performed on the patients at the time of the review. In addition, detailed information on the patients was limited concerning psychiatric and social factors. Follow-up data were frequently missing, including clinical course after dismissal from care facilities and date of death. Finally, there were no available neuroimaging and neuropathology findings to correlate with the clinical evidence.

More recently, Krasnianski et al. [19] published results from their retrospective study of 248 sCJD patients with known molecular subtypes of sCJD, describing the varied psychiatric presentations observed. Noting the difficulties in assessing this population due to varying levels of impairment across the disease trajectory, with most patients displaying aphasia and pronounced dementia, the researchers assert that diagnostic testing becomes severley hampered attenuating the ability to render a correct diagnosis early. Additionally, it was reported that preponderance of CJD surveillance units are managed by neuropathologists, neurologists, and

epidemiologists, and not by psychiatrists, which can impede an early diagnosis, since many cases present with psychiatric symptoms. To date, this has been the largest study of its kind for this particular population with respect to "differences concerning frequency and time point of occurrence of psychiatric symptoms" [19, p. 1209]. This study found that psychiatric symptoms occurred in 90% of patients at disease onset with the following breakdown: 64% displaying agitation, 45% demonstrating hallucinations, 50% with anxiety and 37% exhibiting depression. Interestingly, no illusons were noted early on in the disease. Comparing these findings to existing published data on vCJD, it was found that psychiatric symptoms were more common among the vCJD patients than the sCJD patients, and overall suggest that psychiatric symptoms occur not only early on in vCJD, but also initially among other categories of CJD [19].

In comparing the Wall et al. [5] study with the Krasnianski et al. [19] study, differences are noted in the classification of psychiatric symptoms. In the Wall et al. [5] study, information on depression, anxiety, agitation, and psychotic symptoms were reported. Other indeterminate signs (sleep disturbance) were appraised, but were not included in the Krasnianski et al. [19] study. Additionally, psychotic symptoms in the Wall et al. [5] study included: disorganized thought process, speech, confabulations and perseverations, and depressive symptoms including weight loss. These were not reported in the Krasnianski et al. [19] study.

There were however, similitudes between the studies. Psychiatric symptoms reported in the Krasnianski et al. [19] study were 90%, similar to the results in the earlier study by Wall et al. [5], and, interstingly, the frequency of depression was also comparable. Anxiety and agitation, however, were found to be more common in the Krasnianski et al. [19] study. In light of the fact that psychiatric symptoms are frequently observed in prion diseases of all kinds [5], the authors propose categorizing sCJD as a neuropsychiatric disease, and advise assessing these symptoms as judiciously as one would do for neurological disturbances [19].

4.3. Familial CJD (fCJD)

fCJD also presents with neuropsychiatric symptoms. Yang et al. [6] examined a 75-year old woman with fCJD caused by a point mutation in codon 180 of the PRNP gene. The researchers wanted to demonstrate the need to consider fCJD in patients showing atypical manifestations and MRIs for sCJD even if they presented with a negative family history for dementia. They believe that the slow progress and late onset of fCJD could contribute to a lack of family history. The patient had an 8 month history of progressive dementia and neuropsychiatric symptoms when brought to hospital for examination. The family stated that her symptoms began with depression that included suicidal ideation. The patient then became irritable and paranoid and experienced delusions and visual hallucinations. Antidepressants were not effective in treating her symptoms. At four months prior to hospital admission, the patient developed memory problems that became worse, and was diagnosed with dementia. Upon hospital admission, laboratory studies and physical examination were unremarkable with the exception of minor issues related to walking and clumsiness. Neuropsychological testing showed impaired language functions, attention, memory (visual and verbal), executive, and visuospatial functions. It was also noted that the patient had developed obsessive-compulsive behaviors. After discharge, her CSF tested positive for the 14-3-3 protein, and PRNP sequencing revealed the mutation. Since fCJD has more variation in clinical manifestations that the other categories of CJD, the major problem with this study was that it only examined a single patient. In addition, there were no follow-up examinations after the initial 37-day hospital admission. Although it was reported that the patient was still alive 18 months after onset, the researchers were not able to continue noting symptoms as they appeared in order to better track the disease progress.

One of the largest populations manifesting fCJD are Israeli Jews of Libyan descent where the incidence of CJD is 100 times greater than typically observed [25]. The disorder is attributable to a dominant point mutation at codon 200 of the PRNP gene (E200K) [26]. Prior to the age of 30, the aggregate probability for developing the disorder is rather insignificant, yet the probability increases to 80-100% by the time the person reaches their eighth decade [27]. As with the other categories of CJD, the erraticism with the age of onset coupled with the precipitous onset of symptoms makes it extrememly challenging to identify the specific factors that elicit this form of CJD [16].

In a seminal study focusing on the preclinical neuropsychological symptoms in healthy particpants with inherited risk for CJD, Gigi et al. [16] examined fCJD in 27 Libyan Jews, who were healthy carriers of the E200K gene mutation. The aim of the study was to identify the preclinical neuropsychological signs in both healthy carriers versus non carriers in order to assist physicians in early identification and pathogenesis of the disorder. Homogeneity of the study population was maintained through all participants: having first degree relatives who died from CJD, sharing the same cultural milieu, and having prior knowledge of the symptoms and implications of the disorder. None of the participants or researchers had prior knowledge of the participants'genetic status, which afforded the researchers the ability to perform the study in a double-blind manner. Two groups were formed and labeled carriers and controls. Expansive neuropsychological tests and an anxiety assessment were administered to both groups. Gigi et al. [16] remarked that the E200K familial form has similitude with sCJD, and therefore results from this study had the potential, for the first time, to also elucidate greater insight into the preclinical course of sCJD, which is the most common form of the disease. Results indicated that both healthy groups showed similarity in the demographic mean, with no difference noted when split into age groups. However, a triad of presymptomatic neuropsychological disparities between the two groups were noted. The level of anxiety in the carrier group was significantly greater, and was shown to increase

with the age of the participant, as compared to the control group enlisted from the same families. Cognitively the "old healthy carrier" group shared significant deficits in various tasks of cognition, and included: object recognition, object naming, and the copy stage of the complex figure test. Additionally, the execution of verbal learning, verbal memory and verbal IQ means were distinctively lower between the "old carriers" as compared to the "old controls" (p. 249). Significance was demonstrated only in the slope of the verbal learning task.

The main findings of this study relates to levels of anxiety [16]. Until age 50, anxiety levels were normal with precipitous upsurge thereafter. The authors contend the expression of psychiatric and neurological diseases can result from stressful life events. Furthermore, there are currently some preliminary indices demonstrating that the manifestation of the mutation can be hastened by either psychological or physiologic stress. Gigi et al. [16] assert that the perception of a stressful occurrence is dependant not only on the occurrence, but on individual susceptibility as well. Additionally, there were no reported differences in depression scores between both groups, but a significant difference existed in state anxiety.

The researchers concluded that there are several stages that occur in the carrier population that can herald the onset of the disease. The first stage involves changes in subcortical levels of anxiety and stress, followed by heightened and then diminished concentration and attention, and last by cognitive deficits. Gigi et al. [16] note that although there is a lack of proof to affirm theoretical assumptions to account for this phasic progression, these results portend exciting possibilities for future research on the role of stress in how it might delay the onset of fCJD and possibly sCJD. Moreover, it may assist in generating additional hypotheses for future research on finding a treatment for the disease.

5. Treatment

To date, there are no available cures or therapeutic modalities for CJD or other neurodegenerative disorders, and research is needed to not only better define and delineate symptoms, but also find effective treatments [28-31]. Additionally, there are no preclinical diagnostic tests available to vet affected individuals that are otherwise in good health [30]. While various drugs and treatments have been tested in clinical trials without promising results on symptomology or patient outcome thus far, one positive outcome from these trials has been the display of a collaborative multinational effort in finding an effective treatment modality via a randomized placebo-controlled trial [29]. In the study by Haik et al. [32] on the use of oral doxycycline in CJD diseases, researchers from Italy and France worked symbiotically, despite differences in medical systems and means of enrollment of participants [29]. Unfortunately, while the treatment in the trial showed no survival benefit, it did demonstrate the benefits of instituting international partnerships in employing a rigorous study methodology in researching therapeutic modalities for this progressively fatal degenerative disease, marking this type of collaboration as a template for future research [29].

6. Conclusions

CJD is a progressive terminal neurodegenerative disease and classified within the human prion disorders [16]. Onset is typically precipitous with death occurring within a year of disease onset [3]. While various psychiatric and neurological symptoms have been documented within each category of CJD, the major clinical presentation of the disease is a sudden and progressive dementia [16]. Additionally, misdiagnosis is problematic due to the heterogeneity of presenting symptoms that may not be representative of the initial hallmark signs of the disease. Several case reports in the literature describe diverse psychiatric features upon initial clinical presentation with oftentimes negative, non-specific, results of preliminary supportive tests that have caused affected patients to unfortunately be misdiagnosed [8, 20, 33].

Psychiatric diagnosis is made too often due to the diversity of initial presenting clinical symptoms in tandem with unremarkable supportive tests. A retrospective study [9] assessed 23 cases with either probable or definitive CJD between 2006-2012. Ten of the 23 cases (44%) were first diagnosed with a psychiatric disorder, 6 cases (26%) had a positive family history for CJD and 7 cases (30%) were admitted for psychiatric evaluation. Chuang et al. [34] reported the first case of sCJD in a patient with pre-existing long-term schizophrenia, and detailed how the diagnosis of schizophrenia further complicated and ultimately delayed the diagnosis of sCJD. As a result, it was recommended that a consideration of a diagnosis of sCJD in similar cases when there is a rapid cognitive decline and concomitant psychiatric and neurological symptoms [34].

As illustrated, the initial clinical presentations of CJD are as diverse and multi-faceted as the patients affected, and misdiagnosis is unfortunately common. Probable diagnosis is based on clinical and supportive test (EEG, CSF, MRI) parameters but additional vigilance and repeat testing at various time points is required [20, 35, 36]. In the case report by Chuang et al. [34] it was reported that the patient's initial MRI of the brain was initially interpreted as unremarkable. After the patient began to rapidly decline 8 days after hospital admission, a second MRI of the brain was performed which showed marked hyperintensities. After a retrospective review of the first MRI was performed, it was noted that the hyperintensities clearly demarcated in the second MRI were actually present in the first set of films. The researchers concluded that early positive findings can be missed by even the most experienced clinicians, further complicating early diagnosis [34].

The rise in the occurrence of neurodegenerative disorders and especially CJD has shown to parallel with the increased

longevity across various demographic and geographic strata [28]. Therefore expediency in both the early identification of the disease with proper diagnosis and the identification of Pharmacokinetics or specific treatment modalities that will either cure or prolong survival rates is warranted among this population [28].

While the WHO [22] has stated precipitously advancing dementia and cognitive disorders are vital benchmarks for a probable diagnosis of CJD, Jacquin et al. [17] suggest that the majority of disorders of cognition found in the symptoms of sCJD are vague in the 2009 Consortium criteria. The reason for the missing specific neuropsychological data is due to the rapid disease trajectory that renders the patient to become severely disabled and ultimately die, which then prevents a comprehensive battery of neuropsychological testing to be performed [17, 19]. Therefore, a requisite exists for continued research to ensue that would help to create an evidenced-based repertoire of the dysfunctional cognitive features observed in the initial presentation of the disease, to further assist clinicians in making a correct diagnosis early on. Jacquin et al. [17] concluded that clinical presentations with disorders of cognition, either with or without forfeiture of self-sufficiency, are a key sign of sCJD, yet may emulate other forms of dementia. The inclusion of the WHO [22] criteria and supportive tests in the differential diagnosis, even though the results may be unequivocal, would strengthen the case for a probable diagnosis of CJD [17].

In all of the studies presented, neuropsychiatric symptoms were present before patients were diagnosed with CJD. Whereas vCJD commonly began with depression, withdrawal, anxiety, irritability, insomnia, and loss of interest, sCJD began with sleep disturbances, delusions, paranoia, disorganized speech, hallucinations, depression, agitation, and behavioral changes, and fCJD began with depression, suicidal ideation, irritability, paranoia, and hallucinations. Interestingly, depression was present across the spectrum with irritability, hallucinations, paranoia, and sleep disturbances present in two categories. The preponderance of evidence suggests that utilization of a global approach to early diagnosis is paramount, and that repeated diagnostic investigations are required especially in light of the kaleidoscope of presenting symptoms that may or may not accompany a rapidly progressive dementia in this population.

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