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Understanding Creutzfeldt-Jakob disease in Iran: a systematic review of case reports

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Abstract

Objective: To systematically review the reported cases of Creutzfeldt-Jakob disease (CJD) in Iran.

Methods: A comprehensive literature review of CJD cases in Iran was undertaken using the PubMed®, Scopus® and Google Scholar databases. In addition, the Iranian database MagIran was searched for Persian language reports. Case selection used the following criteria: (i) patients of Iranian origin; (ii) publication in peer-reviewed journals or reputable medical databases; (iii) a definitive diagnosis of CJD based on established diagnostic criteria.

Results: Thirteen cases from twelve reports were included in this systematic review. The majority of the cases were female (11 of 13; 84.6%). The mean ± SD age of patients at hospital admission was 59.38 ± 7.44 years. The findings of the case review suggested that the prevalence of CJD in Iran is not fully established. CJD may be misdiagnosed alongside other clinical signs. The most prevalent early indications of the disease were psychiatric and neurological in nature. A considerable delay in diagnosis was observed in some cases and there was a shortage of brain autopsy records.

Conclusion: Efforts to improve diagnostic capabilities, promote awareness and establish monitoring systems are necessary for managing the challenges of providing an early diagnosis of CJD in Iran.

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Introduction

Creutzfeldt-Jakob disease (CJD) is a rare and fatal neurodegenerative disorder that impacts the human brain and nervous system.[1] Brain cells are impacted by abnormal folding of a typical protein called prion, leading to this condition. The disease can occur in four presentations: spontaneous (or sporadic), inherited (or familial), acquired (or iatrogenic) and variant (vCJD). The sporadic type is the most common, accounting for approximately 85% of cases and typically impacts individuals over 60 years old.[2,3] The inherited genetic form is the result of mutations in the prion protein (Kanno blood group) (*PRNP*) gene and accounts for approximately 10–15% of cases.[4–6] The acquired form is caused by the patient coming into contact with infected tissue, either through medical procedures such as transplants or contaminated surgical instruments, and vCJD can be caused by consuming infected animal products.[7]

Creutzfeldt-Jakob disease is an uncommon illness, with around one case per million people each year.[8] However, it is a deadly illness with a quick course, and there is presently no functional prognosis or cure. The diagnosis of CJD can be difficult, requiring a combination of clinical, laboratory and imaging results. The disease has a distinctive clinical presentation, which includes rapidly developing dementia, coupled with additional neurological symptoms such as ataxia, myoclonus and visual abnormalities.[9–11] Electroencephalogram (EEG) and magnetic resonance imaging (MRI) are essential diagnostic tools, and

the detection of 14-3-3 protein in the cerebrospinal fluid (CSF) can confirm the diagnosis. While CJD is rare, it has significant implications for public health due to its high mortality rate and the potential for iatrogenic spread. Therefore, the aim of this study was to thoroughly examine the case reports and clinical symptoms of CJD in Iran and to enhance understanding of the regional distribution, diagnostic challenges and various clinical presentations of CJD among the Iranian population. Additionally, this systematic review provides important information on the understanding of CJD in Iranian patients, emphasizing the importance of early detection and diagnosis due to the lack of definitive treatments for this rare and fatal neurodegenerative disease.

Materials and methods

Literature review

A systematic literature review was conducted to identify relevant case reports on CJD in Iran. Electronic databases, including PubMed®, Scopus® and Google Scholar, were searched from 1 April 1995 up to 4 August 2023. In this regard, Harzing's Publish or Perish version 8.9.45 was utilized for ease of searching different databases. The search strategy used the following keywords: "Creutzfeldt-Jakob" OR "Creutzfeldt-Jakob Disease" OR CJD, "prion disease*" OR Prion, and "Iran". Accordingly, for Google Scholar, the terms "Creutzfeldt-Jakob" OR "Creutzfeldt-Jakob Disease" OR CJD were searched in the Title

words, and "prion disease*" OR Prion, and "Iran" were searched in Keywords. A same search strategy was used for mining literature in the Scopus® database. For searching PubMed®, the following search strategy was built by MeSH repository and PubMed® Search Builder: (((prion disease [MeSH Terms]) OR (prion diseases [MeSH Terms])) AND (cjd creutzfeldt jakob disease [MeSH Terms])) AND (Iran [Affiliation]). In addition, the Iranian database MagIran (https://www.magiran.com/) was searched for reports on CJD in the Persian language.

Selection of case studies and criteria for reviewed cases

Cases were carefully selected for this systematic review of CJD in Iran, adhering to specific criteria to ensure relevance and accuracy in the analysis. The selection followed a systematic approach, focusing on CJD cases reported in the literature that met the following criteria: (i) patients of Iranian origin; (ii) publication in peer-reviewed journals or reputable medical databases; (iii) a definitive diagnosis of CJD based on established diagnostic criteria.

The selected reports were also checked for the diagnostic criteria used to confirm CJD in cases. The diagnosis of definite CJD was checked based on recognized diagnostic criteria in the field, which included a clinical presentation characterized by rapidly progressive dementia and neurological symptoms, such as ataxia, myoclonus and visual disturbances. Additional findings were considered, which included abnormal MRI or computed tomography (CT) findings, such as brain tissue atrophy and hyperintense signals in specific regions, along with EEG results indicative of abnormal brain electrical activity associated with CJD or the use of CSF to detect specific biomarkers, such as protein 14-3-3 and tau protein, which supported the diagnosis of CJD.

Data extraction and PRISMA report

Two reviewers (A.M. and M.M.) independently conducted the data extraction. In the event of any discrepancies, a third author (M.H.) resolved the issue. Information collected included patient demographics, clinical presentation, diagnostic criteria, medical history and family history. To illustrate the systematic case selection process, a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was generated. The flowchart depicts the number of articles identified, screened, assessed for eligibility and included in the final analysis, following the PRISMA guidelines.

Results

The PRISMA flow diagram presents the systematic approach taken in this literature review, ensuring transparency and reproducibility of the case selection process (Figure 1).

Thirteen cases from twelve studies were included to extract information for investigating CJD in Iranian patients (Table 1).[8,12–22] The mean ± SD age of the 13 cases was 59.38 ± 7.44 years. The regional distribution of CJD cases in Iran, encompassing areas such as Tabriz, Mashhad, Tehran, Rafsanjan and Babol, indicates potential regional factors influencing CJD incidence and diagnosis. Noteworthy is the predominance of cases from Northern regions, emphasizing the importance of considering geographic influences on CJD diagnoses. This geographic distribution underscores the importance of considering potential regional factors that may influence CJD incidence and diagnosis. The clinical management of CJD is complicated by variations in the timing of diagnosis and
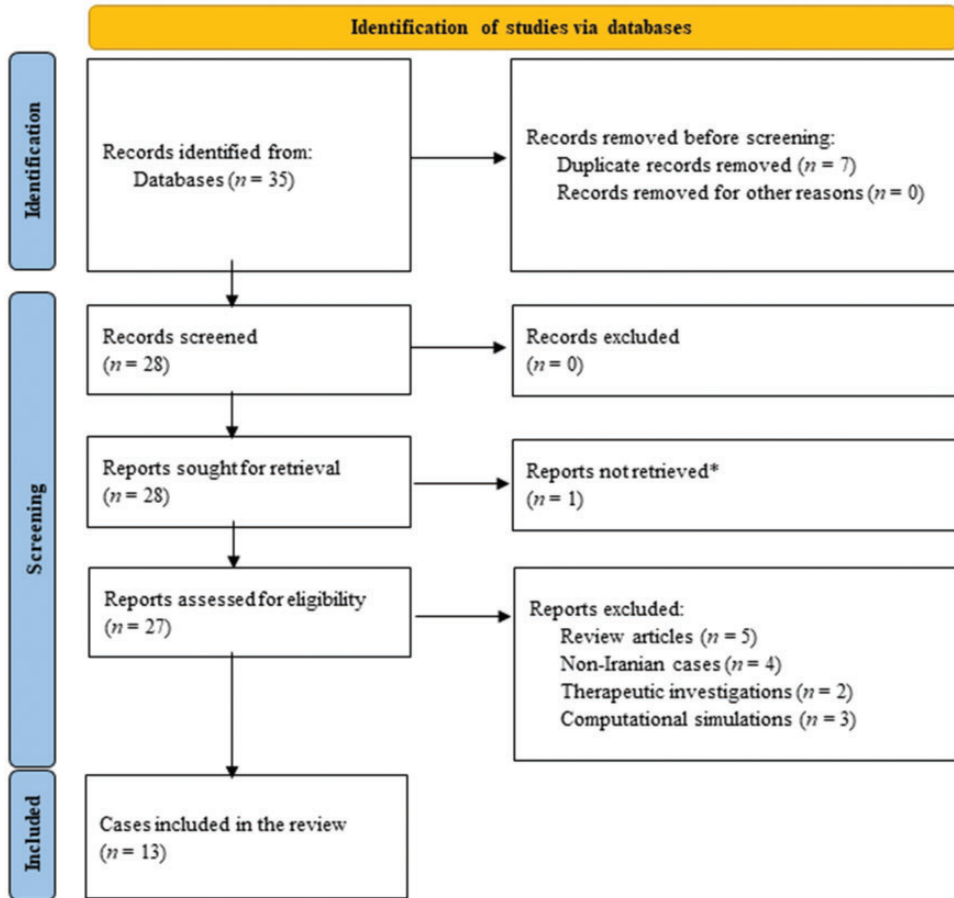
Figure 1. PRISMA flow diagram showing the systematic case selection process for a systematic literature review on Creutzfeldt-Jakob disease (CJD) in Iran. The flowchart outlines the number of articles identified, screened, assessed for eligibility and included in the final analysis. *One study entitled "Creutzfeldt-Jakob disease in an Iranian: the first clinico-pathologically described case" was not retrieved due to not finding a working link to the paper.

subsequent patient outcomes. Incomplete or unmentioned data for cases such as Patient-1, -3, -7 and -8, coupled with differing survival periods (e.g. 9 months for Patient-4 and -5; 12 months for Patient-6), underscores the challenge in managing CJD.

The varied symptoms of the disease and the absence of specific diagnostic tests lead to delays or incorrect diagnoses (Table 2).[8,12–22] Diagnosing CJD is difficult because its symptoms can imitate other neurological or mental health disorders. Patients with a final diagnosis of CJD exhibited cognitive impairment, which is consistent with the most common sporadic subtype of CJD. Accordingly, Patient-1 initially presented with depressive symptoms, confusion, disorientation, insomnia, loss of appetite, periodic agitation, anxiety, delusions, reduced interest in activities, catatonic stupor and complete muteness, which led to the referral for neuropsychological

Table 1. Clinical and demographic data for 13 patients diagnosed with Creutzfeldt-Jakob disease (CJD) in Iran.[8,12–22]

Patient number	Age at examination, years	Sex	Date of CJD diagnosis	Date or time of death	Region in Iran	Reference
Patient-1[a]	56	F	October 2003	November, 2003	Tabriz[b]	[16]
Patient-2	71	F	May, 2004	June, 2004	Tabriz[b]	[15]
Patient-3	70	F	1996	Not specified	Mashhad	[17]
Patient-4	50	F	Not specified	Nine months after onset of symptoms	Tehran	[19]
Patient-5	58	F	2016	Nine months after onset of symptoms	Rafsanjan	[22]
Patient-6	59	F	Not specified	One year after diagnosis	Rafsanjan	[22]
Patient-7[c]	57	M	December 2020	On the 20th day of hospitalization	Tehran	[21]
Patient-8	48	F	Not specified	Not specified	Babol	[8]
Patient-9	56	F	Not specified	Not specified	Tehran[d]	[13]
Patient-10	61	M	Not specified	45 days after admission	Isfahan	[20]
Patient-11	52	F	Not specified	Not specified	Tehran	[12]
Patient-12	72	F	Not specified	The patient was discharged in a vegetative state, but the time of death was not specified	Tabriz	[14]
Patient-13	62	F	Not specified	Not specified	Tehran	[18]

[a]The patient presented with depressive symptoms, confusion and disorientation over a period of 3 months before her admission to the hospital.
[b]Patient-1 and patient-2 were from same hospital in Tabriz city.
[c]The patient was referred to the hospital with symptoms and there were no records on when his symptoms began.
[d]The patient was originally from Mashhad.
F, female; M, male.

assessments and a subsequent diagnosis of sporadic CJD.[23] Similarly, Patient-5 presented with dementia, depression, muscle twitches, limb stiffness, loss of physical strength, and became bedridden, which are typical features of sporadic CJD.[19] However, not all patients with CJD exhibit cognitive symptoms as the initial presentation. Patient-2 had visual symptoms, transient confusion and disorientation, dystonic posture in the right arm, transient attacks of agitation, hallucinations, confusional state, macropsy, micropsy, blurred vision, colour vision disturbance and mild left-sided hemiparesis, which led to an initial diagnosis of cerebral infarction, but a final diagnosis of CJD.[16] Patient-3 had a medical history of both ischaemic stroke and ischaemic heart disease, initially raising concerns that her age of 70 years might be a contributing factor to her presenting symptoms, which resembled those of a minor stroke. However, further clinical presentations, including lethargy, speech disturbance, generalized weakness, myoclonic jerks, unusual behaviour, emotional incontinence, inappropriate crying, and further tests led to a final diagnosis of CJD.[15]

The non-specific nature of CJD symptoms increases the risk of misdiagnosis (Table 3).[8,12–22] Patient-4's initial suspicion of Chiari malformation[15] and Patient-7's diagnosis of an acute psychotic episode underscore the challenge in distinguishing

Table 2. Symptom data for 13 patients diagnosed with Creutzfeldt-Jakob disease (CJD) in Iran.[8,12–22]

Patient number	Symptoms	Reference
Patient-1	Depressive symptoms, confusion, disorientation, insomnia, loss of appetite, periodic agitation, anxiety, delusions, reduced interest in activities, catatonic stupor, complete muteness	[16]
Patient-2	Visual symptoms, transient confusion and disorientation, dystonic posture in right arm, transient attacks of agitation, hallucinations, confusional state, macropsia, micropsia, blurred vision, colour vision disturbance, mild left-sided hemiparesis	[15]
Patient-3	Lethargy, speech disturbance, generalized weakness, myoclonic jerks, unusual behaviour, emotional incontinence, inappropriate crying, recent memory loss	[17]
Patient-4	Tinnitus, vertigo, ataxia, myoclonic jerks, speech impairment, difficulty in swallowing, cognitive impairment	[19]
Patient-5	Dementia, depression, muscle twitches, limb stiffness, loss of physical strength, bedridden	[22]
Patient-6	Imbalance, ataxia, muscle and organ spasms, swallowing disorder, reduced communication, silent, uncommunicative	[22]
Patient-7	Severe agitation, disorientation, impaired consciousness, headache, diplopia, myalgia, unsteady gait, obsessive thoughts, fear of death, verbal and physical aggression, depressed mood, psychomotor retardation, insomnia, anorexia, visual and auditory hallucinations, delusions of persecution, cognitive decline	[21]
Patient-8	Depressed mood, loss of appetite, insomnia, mutism, ataxia, slowness of movements, dysarthria, rigidity, uncontrollable movements of the limbs, loss of performance, staring at a point and screaming horribly, negativism and echolalia, myoclonus	[8]
Patient-9	Confusion, progressive mental deterioration, hallucination, myoclonic jerks, impaired memory, incontinence, dysphagia, motor abnormalities, loss of speech, severe muscle stiffness	[13]
Patient-10	Problems of comprehension, psychomotor condition, drowsiness, apathetic affect, decreased speech output, visual hallucination, negative attitude, concrete thinking, impaired judgement, augmentation of muscle tone (rigidity), spontaneous myoclonus involving entire body, impaired pursuit gaze, asterixis, ataxic gait, kinetic mutism (developed after 15 days)	[20]
Patient-11	Memory problems, forgetting names of family members, progressive visual hallucinations, sharp decline in cognitive abilities, sharp decline in verbal abilities, sharp decline in motor abilities, acute mood problems, proposals for electrical convulsions, double urinary and faecal incontinence, loss of ability to speak, lack of recognition of individuals and objects, gradual inability to walk, staying in bed all the time, development of a lower lumbar bed sore, severe stiffness of the extremities, muscle jerking in the upper extremities, stupor condition, lack of obedience to orders, normal and symmetrical pupil reflex to light, normal fundoscopy, brief limb movement with painful stimulation, intensified deep tendon reflexes (grade $+3$), down plantar reflex, severe and generalized limb stiffness, intermittent muscle jerking in both upper limbs	[12]

(continued)

Table 2. Continued.

Patient number	Symptoms	Reference
Patient-12	Behavioural changes, rapidly progressive dementia, disorientation to time and place, repetitive speech, anomia, impaired comprehension, myoclonic jerks, loss of smell, fever, obsessive behaviours, inability to recognize family members, aimless looking around, anomia and impaired comprehension, lack of expression of hunger/thirst	[14]
Patient-13	Rapidly progressive dementia, myoclonus, visual problems, akinetic mutism	[18]

CJD from other neurological or psychiatric conditions. Patient-11,[12] initially received antidepressants, further exemplifies the risk of overlooking CJD in the absence of specific diagnostic markers. Therefore, the diagnosis of CJD is challenging due to its varied symptoms, which can mimic other neurological or psychiatric conditions. Moreover, the lack of definitive diagnostic tests further complicates the diagnosis. Consequently, it is essential to consider CJD in the differential diagnosis of patients presenting with cognitive, neurological or psychiatric symptoms, especially in younger patients.[8] These variations in diagnostic time and survival emphasize the need for early recognition of CJD symptoms and better understanding of factors contributing to disease progression, aiding clinicians in providing more effective support and care to patients and their families.

Table 3 provides diagnostic insights garnered from the 13 cases ultimately diagnosed with CJD. These patients were initially diagnosed with a range of different conditions, including depression, multiple lacunar infarctions, senile atrophy, acute disseminated encephalomyelitis (ADEM), acute psychotic episodes, major depressive episodes with catatonia, and even neuroleptic malignant syndrome (NMS). However, their final diagnoses were CJD, highlighting a conclusive diagnosis can be established by combining clinical symptoms, imaging and laboratory tests. A post-mortem examination is essential in definitively diagnosing CJD. Only three patients (Patient-1, Patient-2 and Patient-3) underwent post-mortem examinations to verify CJD. All three patients were from different locations in Iran: Patients 1 and 2 were from Tabriz, East Azerbaijan Province, while Patient 3 was from Tehran.

The 13 patients with CJD exhibited diverse medical histories, ranging from no significant past medical history to conditions like ischaemic heart disease, benign prostatic hyperplasia and splenectomy (Table 4).[8,12–22] Furthermore, family history appears to play a role in some cases as well. Patient-7 had a family history of schizophrenia and benign prostatic hyperplasia, while Patient-8 had a positive family history of depressive symptoms reported in her mother, along with a history of distress and depressive symptoms after a stressor, and a splenectomy due to a car crash 17 years prior to admission. Patient-3 had previously been diagnosed with atrial fibrillation and ischaemic heart disease. It is uncertain whether Patient-4's Chiari malformation surgery could be resulted in neurological symptoms. Nevertheless, a comprehensive medical background and clinical assessment can aid in determining the disease. When it comes to CJD, a family history can suggest a genetic inclination towards the illness. On the other hand, previous medical background and surgical procedures can assist in excluding different

Table 3. Initial diagnostic information obtained for 13 patients who received a final diagnosis Creutzfeldt-Jakob disease (CJD) in Iran.[8,12–22]

Patient number	Initial diagnosis	Final diagnosis	Imaging tests	Other diagnostic tests	Autopsy confirmation	Reference
Patient-1	Depression	CJD	CT and MRI (normal)	EEG: generalized background slowing with a few irregular sharp waves	Yes	16
Patient-2	Multiple lacuna and cerebral infarctions, senile atrophy	CJD	Brain CT and MRI: multiple lacunar infarctions, senile atrophy	EEG: generalized slow sharp waves, progressive slowness and periodic sharp waves, slow and disorganized background activity interrupted by repetitive discharges of large sharp waves	Yes	15
Patient-3	Minor stroke	CJD	Brain CT: mild atrophy,	CSF analysis: no cell abnormalities, normal glucose concentration, normal protein level, EEG	Yes	17
Patient-4	Chiari malformation (considered)	sCJD	MRI (DWI, T2-weighted, FLAIR)	CSF analysis: positive 14-3-3 protein; and EEG	No	19
Patient-5	Dementia and depression	sCJD	MRI (DWI, T2-weighted, ADC, T1-weighted)	Blood tests: high blood sugar; and EEG	No	22
Patient-6	ADEM	sCJD	CT, MRI	EEG	No	22
Patient-7	Acute psychotic episode, major depressive episode with catatonia	CJD	MRI	Blood tests, urinalysis, and EEG	No	21
Patient-8	Catatonia, NMS	CJD	MRI (hypersignality in caudate and putamen)	Lumbar puncture (routine analysis normal); CSF analysis: protein 14-3-3 identified; and EEG	No	8
Patient-9	CJD	CJD	MRI	EEG, clinical findings, ruled out other dementing disease	Yes	13

(continued)

Table 3. Continued.

Patient number	Initial diagnosis	Final diagnosis	Imaging tests	Other diagnostic tests	Autopsy confirmation	Reference
Patient-10	CJD	CJD	EEG and MRI	Liver function tests, blood culture, serum HIV antibody tests, serum and CSF HSV–PCR, CSF cytology, thyroid survey, serum vitamin B12 and lithium levels, CSF VDRL, CSF India ink test	Yes	20
Patient-11	Memory problems, forgetting names of family members, visual hallucinations, cognitive decline, verbal decline, motor decline	CJD	Brain MRI: DWI (hyperintensity and hypersignality in right caudate nucleus and parieto-occipital cortex – ribbon sign)	Evaluation by a psychiatrist, acute mood problems, proposed electrical convulsions, urinary and faecal incontinence, loss of speech, stiffness, muscle jerking	No	12
Patient-12	COVID-19	CJD	MRI: initial MRI (1 October 2020): no abnormality; second MRI (5 October 2020): abnormal signal intensity at bilateral parieto-occipital cortices with restriction of diffusion on DWI; third MRI: bilateral cortical restricted diffusion in posterior aspects of parietal lobes and parietoccipital regions, and some restriction in the left frontal cortex	EEG (12 October 2020): mildly slow background rhythm; subsequent EEGs (24 October 2020 and 10 November 2020): periodic sharp wave complexes Nasal and CSF PCR tests negative for COVID-19. High level of LDH in CSF	No	14

Table 3. Continued.

Patient number	Initial diagnosis	Final diagnosis	Imaging tests	Other diagnostic tests	Autopsy confirmation	Reference
Patient-13	Rapidly progressive dementia syndrome	CJD	Diffusion-weighted MRI showed water restriction in right frontal and parietal lobes ('ribbon sign') and bilateral caudate nuclei	EEG revealed periodic 1–2 Hz sharp wave complexes with a generalized distribution in both hemispheres. Routine CSF analysis showed no abnormality in cell count and chemistry	No	18

CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; CSF, cerebrospinal fluid; sCJD, sporadic CJD; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; ADC, apparent diffusion coefficient; ADEM, acute disseminated encephalomyelitis; NMS, neuroleptic malignant syndrome; HIV, human immunodeficiency virus; HSV-PCR, herpes simplex virus-polymerase chain reaction; VDRL, venereal disease research laboratory; PCR, polymerase chain reaction; COVID-19, coronavirus disease 19; LDH, lactate dehydrogenase.

neurological disorders with similar symptoms. Patient-4 with Chiari malformation had a medical history taken into account during the initial diagnosis, but it was later disregarded as the patient displayed indications of CJD in other diagnostic examinations. Medical issues like elevated blood glucose and benign prostatic hyperplasia may not be directly linked to CJD but can offer more details on the patient's general health condition.

Creutzfeldt-Jakob disease is an uncommon, quickly advancing neurodegenerative condition impacting the brain, causing severe neurological symptoms and ultimately resulting in death. At present, there is no definitive treatment for CJD, with treatment approaches primarily concentrated on symptom management and providing supportive care. As presented in Table 5, the treatment approaches for the 13 CJD patients were predominantly focused on providing symptomatic and supportive care, such as utilizing antidepressants, antipsychotics, and electroconvulsive therapy.[8,12–22] Yet, the effectiveness of these treatments was limited, with only a subset of the patients displaying improvements, while others encountered issues such as myoclonic seizures, aspiration pneumonia and sepsis. Additionally, the administration of antipsychotic medications to individuals with CJD has been linked to the onset of NMS, a rare but serious condition necessitating prompt intervention.

Discussion

Creutzfeldt-Jakob disease is a rare, fatal, neurodegenerative disease that inhibits brain function. CJD is divided into four categories based on clinical, pathological and genetic characteristics as follows: spontaneous (or sporadic), inherited (or familial), acquired (or iatrogenic) and vCJD. Despite its rarity, CJD poses a significant

Table 4. Medical history for 13 patients diagnosed with Creutzfeldt-Jakob disease (CJD) in Iran.[8,12–22]

Patient number	Family history	Medical history	Previous interventions	Other medical problems	Reference
Patient-1	Negative for similar disorder	Negative for similar disorder, surgery, and any other medical problems	Negative	Negative	16
Patient-2	N/A	No specific medical history	N/A	N/A	15
Patient-3	N/A	Ischaemic heart disease, atrial fibrillation	N/A	N/A	17
Patient-4	N/A	Chiari malformation (considered), surgery candidate	Surgery (unknown)	None	19
Patient-5	N/A	Normal except for high blood glucose	None	High blood glucose	22
Patient-6	N/A	N/A	N/A	N/A	22
Patient-7	Family history of schizophrenia	Benign prostatic hyperplasia, family history of schizophrenia	N/A	N/A	21
Patient-8	Positive family history of depressive symptoms in her mother	Splenectomy following a car crash 17 years ago, referred to a psychiatrist in 1988 because of distress and depressive symptoms following a treated stressor	Splenectomy following a car crash 17 years ago	N/A	8
Patient-9	Parents, nephew, niece	No specific medical history	Multiple instances of non-sterile phlebotomy, traditional methods	Negative	13
Patient-10	Negative	No history of neurological disease	No previous interventions	Negative	20
Patient-11	Negative	No prior history of medication use. No history of epilepsy or cerebrovascular problems. No history of psychiatric or neurological disorders	The patient had undergone a dental procedure approximately 6 weeks prior to the onset of symptoms	Negative	12
Patient-12	N/A	Complained of fever and loss of smell about 30 days before hospitalization	Hospitalized and treated with high-dose corticosteroids, plasmapheresis (250 ml/kg) and intravenous immunoglobulin	COVID-19	14
Patient-13	Negative	N/A	N/A	N/A	18

N/A, not available.

Table 5. Treatment information for 13 patients diagnosed with Creutzfeldt-Jakob disease (CJD) in Iran.[8,12–22]

Patient number	Initial treatment	Other treatment	Improvement	Complications	Reference
Patient-1	Antidepressants (nortriptyline 75 mg/day and haloperidol 0.5 mg/day)	ECT	Some improvement, but eventually deteriorated	Intubation for airway support	16
Patient-2	Haloperidol and clonazepam	None	No beneficial effect, condition became progressively worse	Myoclonic seizures, intubation	15
Patient-3	N/A	N/A	N/A	Progressive neurological abnormalities, deteriorated breathing, probably associated cardiac problems without a significant response to medications and supportive treatment	17
Patient-4	N/A[a]	N/A	None	None	19
Patient-5	N/A	N/A	None	Aspiration pneumonia and sepsis	22
Patient-6	Hospitalization, supportive care	N/A	N/A	Aspiration pneumonia and sepsis	22
Patient-7	Symptomatic treatment, ECT	N/A	N/A	N/A	21
Patient-8	Medications prescribed by a neurologist: fluphenazine decanoate, venlafaxine, sodium valproate, duloxetine, olanzapine, trihexyphenidyl	Moderate worsened symptoms and led to referral to a psychiatric hospital ECT with diazepam administered four times before the ECT Serum therapy and urine catheterization conducted to modify inadequate fluid intake and low urine volume	N/A	NMS due to long-term antipsychotic medications, rigidity, fever, and elevated CPK and LDH Admitted to ICU due to decreased consciousness Protein 14-3-3 identified in the cerebrospinal	8

Table 5. Continued.

Patient number	Initial treatment	Other treatment	Improvement	Complications	Reference
		Levetiracetam 500 mg twice a day and sodium valproate 400 mg twice a day prescribed to resolve muscle spasms and myoclonus of the patient		fluid, and the diagnosis of CJD was confirmed in the patient	
Patient-9	N/A	N/A	N/A	N/A	13
Patient-10	N/A	No other specified treatments	Deteriorated	None	20
Patient-11	The patient was advised to take antidepressant medication but did not take them.	N/A	N/A	The patient developed double urinary and faecal incontinence, lost the ability to speak, had severe stiffness of the extremities, muscle jerking in the upper limbs, and a lower lumbar bed sore.	12
Patient-12	Treated with high-dose corticosteroids (2 g/kg), plasmapheresis (250 ml/kg) and intravenous immunoglobulin	Treatment with valproate and levetiracetam for myoclonic seizures	None	Worsening of myoclonic seizures during hospital confinement	14
Patient-13	N/A	N/A	N/A	N/A	18

[a]Not specified.

ECT, electroconvulsive therapy; N/A, not available; NMS, neuroleptic malignant syndrome; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; ICU, intensive care unit.

public health risk because of its high mortality rate and the lack of a cure or effective treatment. CJD is difficult to diagnose; and patients may be misdiagnosed with depression, bipolar catatonia, metabolic encephalopathy, autoimmune encephalitis, ischaemic stroke, cerebrovascular accident, toxic insults, Lewy body or Alzheimer's dementia, vitamin B12 and/or folate deficiency dementia, multiple lacunar infarctions and senile atrophy or ADEM. According to this current literature review, the initial clinical indications are typically unclear, making early identification challenging. This is confirmed by the first patient initially diagnosed with depression but was later diagnosed with bipolar catatonia. Similarly, the second patient was diagnosed with many lacunar infarctions and senile atrophy, and the ultimate diagnosis was spongiform encephalopathy. As a result, persons with rapidly worsening neurological symptoms and cognitive decline should have CJD considered in their differential diagnosis.

The lack of precise diagnostic tests complicates the difficulty of accurately identifying CJD. So, accurate diagnosis usually requires the use of a variety of diagnostic tests, such as imaging techniques, cerebrospinal fluid analysis and electroencephalography. Although medical history provides important information, a comprehensive clinical assessment, which includes neurological tests, is essential for making an accurate diagnosis of CJD. The combination of family background, previous medical issues and surgeries, together with clinical evaluations, helps in gaining a comprehensive understanding of the patient's health.

The use of clinical symptoms, imaging (CT and MRI), EEG and cerebrospinal fluid examinations have all been found to be useful in the diagnosis of CJD-related brain tissue injuries. MRI, CT and other imaging modalities while valuable in detecting CJD-related brain changes, such as atrophy and hyperintense signals in the caudate nucleus, putamen, and cortex, may not provide absolute certainty of a diagnosis of CJD. Post-mortem examination, conducted in only a few cases, remains crucial for a definitive diagnosis of CJD, emphasizing the need for improved diagnostic tools. Advances in genetics and genomic medicine may present new insights into the mechanisms behind CJD and other prion disorders. The development of novel biomarkers and imaging tools may aid in the disease's early identification and diagnosis. Biomarkers such as increased amounts of 14-3-3 and Tau proteins in CSF have also been associated to CJD.[11] Furthermore, genetic testing on variations of the PRNP gene have been identified as potential indicators for prion diseases. For example, research on human prion diseases focused on the PRNP gene and its variations at codon 129 have emphasized its influence on vulnerability, medical progression and molecular subtypes of sporadic CJD in East and South Asian communities.[3] The effects of PRNP gene polymorphic heterozygosity at codons 129 and 219 on different types of CJD differ, with significant results seen in 129 MV and 219EK heterozygosity.[24] The importance of genetic testing for diagnosis is highlighted in a case study of a Chinese man with a homozygous E200D mutation in the PRNP gene.[25] The case report also examined how PRNP mutations such as E200K, V180I, M232R and P102L affect inherited prion diseases, impacting the timing and development of the disease in various ways.[25] More research should be conducted on the role of the PRNP gene in different CJD subtypes to improve diagnosis, prognosis and potential treatments for prion diseases.[26] Hence, studying PRNP gene variations could aid in the prompt detection of CJD in future studies involving Iranian individuals exhibiting neurodegenerative symptoms.

Managing patients with CJD can be difficult due to the absence of effective available treatments. Despite testing multiple drugs in both preclinical and clinical trials, none have proven to be effective in stopping or reversing the progression of the disease. Current potential treatments being explored involve immunotherapies and RNA-based therapies that target the abnormal prion proteins causing the illness.[27,28] Immunotherapy, in which monoclonal antibodies are used to target the aberrant prion protein responsible for CJD, is one potential therapeutic option.[29] Monoclonal antibodies, such as PRN100, are being studied for their efficacy in treating CJD.[28] Antisense oligonucleotides (ASOs) are another interesting treatment option for CJD.[30] ASOs are synthetic compounds that attach to particular RNA molecules, causing them to degrade or hinder protein production. ASOs have been demonstrated to be successful in lowering the amounts of aberrant prion protein in CJD mice models,[27] suggesting that they might be used as a therapy option for the condition. Furthermore, stem cell therapy is a viable therapeutic option for CJD.[31,32] According to research, mesenchymal stem cells exhibit anti-inflammatory and neuroprotective qualities that may be useful in the treatment of CJD. In addition, human induced pluripotent stem cells produced from the skin cells of CJD patients might be utilized to build disease models and evaluate possible therapeutic agents.[33,34] Difficulties in disease diagnosis led to delays in treatment. Early detection is essential in order to offer improved assistance and attention to patients and their families, even when a curative solution is not available.

In order to diagnose CJD, a complete medical history and physical examination, as well as diagnostic methods such as MRI, EEG, CSF investigation and the assessment of *PRNP* gene polymorphisms, are required. The medical history of CJD patients varies and may or may not be relevant to the disease's development. Some of the cases in the current study had a family history of neurological or psychiatric problems, whereas others had no medical history or had undergone surgery. As a result, a thorough medical history and physical examination, as well as diagnostic tools, are critical in detecting CJD and advancing our understanding of disease genesis and development. This current study has described thirteen patients with CJD in Iran and the findings provide insight into some of the difficulties involved with the identification and reporting of CJD patients in the region, such as delayed clinical symptom onset, diagnostic complexity and the likelihood of unreported cases. While this current research provides useful insights into these specific cases, it is critical to note that determining the exact prevalence of CJD in Iran would be a complicated task. Population-based epidemiological studies are required to gain a comprehensive understanding of the true prevalence and occurrence of CJD in Iran. This type of study could reveal the underlying factors contributing to underdiagnosis, underreporting and the potential presence of unidentified cases. Furthermore, due to factors such as low awareness and comprehension among healthcare personnel, limited access to specialist diagnostic equipment, a lack of established surveillance systems and cultural barriers, identifying CJD in Iran remains challenging. These problems might lead to delayed or missed diagnoses, as well as inadequate case reporting. To overcome these challenges and increase CJD diagnosis in Iran, efforts must be made to promote awareness, enhance diagnostic capacity, create surveillance systems and educate healthcare professionals and the general public.

Author contributions

interpretation, and drafted the manuscript. Parastoo Motamedaria: contributed to data collection and analysis, and manuscript drafting. Malihe Naderi: participated in the systematic review process, contributed to data analysis, and interpretation of the findings from the cases. Mina Hassanpour: contributed to the literature review and data extraction. Zahra Salavatiha and Mahsa Makouei: assisted in data organization and importing data, and contributed to the manuscript's methodology section. Angila Ataei-Pirkooh: contributed to the study's conception, design, supervision, and interpretation, as well as critical revision of the manuscript.

Declaration of conflicting interest

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