Ataxia as an initial presentation of Sporadic Creutzfeld – Jakob disease : an atypical case report and literature review

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Abstract:

Sporadic Creutzfeldt Jakob disease is a rare, fast-progressing neurodegenerative disease with a fatal outcome. Even though its treatment options are scarce, and there is no cure for the disease, adequate diagnosis can help patients and their families come to terms with the disease on time, and give them valuable time to plan accordingly. We report a case of a patient presenting to our emergency department with a 2-week history of ataxia, and oscillopsia. Her initial neurological examination revealed subtle dysarthria, diplopia with left gaze, wide-based ataxic gait with occasional small steps, sinistropulsion in the Romberg position, and ataxia of the limbs, predominantly of the left arm. The patient at that time did not exhibit cognitive impairment, movement disorders, or other neurological signs. Her initial brain MSCT was without lesions or other pathomorphological supstrate. During hospitalization, treatable causes were firstly excluded with blood and CSF lab tests excluding metabolic, toxic, infectious, autoimmune, and paraneoplastic causes. Detailed medical history revealed subtle personality changes, while cognitive testing revealed moderate cognitive impairment. Brain MRI and EEG 4 days after hospitalization reported typical changes seen with advanced prion disease surprisingly being the fact that the patient had a mild to moderate clinical picture. RtQuIC analysis of the CSF was performed to prove probable sCJD and was positive. The patient's family were given instructions, while the wishes of the patient, and family members were fulfilled concerning planning future care. Afterward, the patient's state deteriorated rapidly as per the tragic prognosis of sCJD resulting in akinetic mutism, and death. Ataxia without cognitive impairment, rigor, or movement disorders is an uncommon clinical presentation for a disease with a 1:1 000 000 incidence rate. Modern diagnostic methods in way of more advanced brain MRI capabilities, and RT-QuIC obviate the need for complicated, and potentially infectious brain biopsy in diagnosing sCJD. Alongside the case report, we present a short but comprehensive literature review of modern data regarding the sCJD. This case report and literature review serve to educate clinicians about this rare but devastating disease.

Keywords: ataxia, Creutzfeld – Jakob disease, rare disease

Sažetak:

Ataksija kao početna manifestacija sporadične Creutzfeld-Jakobove bolesti: atipični prikaz slučaja i pregled literature

Sporadična Creutzfeldt Jakobova bolest je rijetka, brzo napredujuća neurodegenerativna bolest sa smrtnim ishodom. Iako su mogućnosti liječenja oskudne, bez etiološke mogućnosti liječenja, adekvatna

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dijagnoza može pomoći pacijentima i njihovim obiteljima da na vrijeme prihvate bolest te im dati dragocjeno vrijeme za planiranje u skladu s nepovoljnom prognozom. Predstavljamo slučaj pacijentice koja se prezentirala u našoj hitnoj službi s 2-tjednom poviješću ataksije i oscilopsije. Njezin inicijalni neurološki pregled otkrio je suptilnu dizartriju, diplopiju s lijevim pogledom, široki ataksični hod s povremenim malim koracima, sinistropulziju u Rombergovom položaju i ataksiju udova, pretežno lijeve ruke. Pacijentica u to vrijeme nije pokazivala kognitivno oštećenje, poremećaje pokreta niti druge neurološke znakove. Njezin početni MSCT mozga nije ukazivao na patomorfološki supstrat. Tijekom hospitalizacije uzroci koji se mogu liječiti najprije su isključeni laboratorijskim pretragama krvi i likvora, isključujući metaboličke, toksične, infektivne, autoimune i paraneoplastične uzroke. Detaljna povijest bolesti otkrila je suptilne promjene osobnosti, dok je kognitivno testiranje otkrilo umjereno kognitivno oštećenje. MR mozga i EEG 4 dana nakon hospitalizacije prikazali su tipične promjene uočljive kod uznapredovale prionske bolesti, što je iznenađujuća činjenica s obzirom da je pacijentica imala blagu do umjerenu kliničku sliku. Provedena je RT-QuIC analiza likvora kako bi se dokazao vjerojatni sCJD koja pristiže pozitivna. Date su upute obitelji bolesnice te su ispunjene želje bolesnice i članova obitelji oko planiranja buduće njege. Nakon hospitalizacije, stanje pacijentice se brzo pogoršalo prema tragičnoj prognozi sCJD-a te je rezultiralo akinetičkim mutizmom i smrću. Ataksija bez kognitivnog oštećenja, ukočenosti ili poremećaja pokreta neuobičajena je klinička slika bolesti koja ima stopu incidencije 1:1 000 000. Suvremene dijagnostičke metode u smislu naprednijih mogućnosti MR mozga i RT-QuIC uklanjaju potrebu za kompliciranom i potencijalno infektivnom biopsijom mozga u dijagnosticiranju sCJD-a. Uz prikaz slučaja donosimo kratak, ali sveobuhvatan pregled literature o suvremenim podacima o sCJD-u. Ovaj prikaz slučaja i pregled literature služe za edukaciju kliničara o ovoj rijetkoj, ali razornoj bolesti.

Ključne riječi: ataksija, Creutzfeld – Jakobova bolest, rijetke bolesti

Introduction

Creutfeldt-Jakob disease (CJD) or spongiform encephalopathy is a rare, fast-progressing neurodegenerative disease caused by an accumulation of an abnormally folded proteinaceous substance called a prion. It is a dangerously transmissible, and uniformly fatal disease. (1,2). "Prions" named by Professor Stanley B. Prusiner are an abnormal isoform (PrPsc – sc meaning "scrapie") of a normal cellular membrane protein of undetermined function (PrPc). Their unnatural state is caused by conformational changes in their structure in which the degree of helical proportion diminishes while its β pleated sheet increases. This triggers a "domino effect" in which normal human prion proteins PrPc change their shape when in contact with the abnormal prion protein, making CJD a conformational disease. These abnormal proteins are protease resistant (in various percentages) causing accumulation and with it neuronal death, gliosis, and vacuolation with atrophy hence the name "spongiform" (1). Depending upon the destruction of a particular part of the brain (be it frontal, parietal, occipital, temporal cortex or basal ganglia, thalamus, or cerebellum), genetic variant in 129 codon on 20. chromosome, and molecular prion type (MM1, MM2, VV1, VV2, MV1, MV2) or the cause of initial prion accumulation there are various clinical presentations. All of that makes the correct diagnosis even more difficult. Different causes of initial prion coming of existence is what differentiate CJD into sporadic (85% of cases, etiology unknown), hereditary (10-15%), acquired disease (less than 1%) (kuru, iatrogenic, and variant). Even though sCJD is the most represented form of CJD its rarity is attested by the fact that its annual incidence is 1 to 2 cases per million of the population worldwide, and in the case of sCJD there has been a small predominance in women (1,4:1 compared to men) (2). However, its rarity does not excuse an astute clinician from not recognizing this devastating disease as its quick destructive potential on a patient and his/hers family with all treatments failing cause a leaving mark on all of those included. SCJD is most often diagnosed in elderly patients with an age of onset being between 55 and 75 years, while a median disease duration is 6 months, with patients usually expiring in the terminal stage from respiratory infection (2). Depending on presentation at the onset the symptoms of sCJD are fast cognitive decline (72% of patients at onset), ataxia (72% onset), pyramidal symptoms (40% onset), myoclonus (40% onset), extrapyramidal symptoms (36% onset), visual disturbances (38% onset), paresthesia (13% onset), akinetic mutism (9% onset), and epileptic seizure (3% onset) (2). Divergence from the typical sCJD clinical picture should not lead a clinician from a diagnostic path as atypical variations of sCJD such as the Heidenhaim variant (prominent central visual symptoms such as anopia) and Brownell-Oppenheimer variant (cerebellar ataxia as an only neurological symptom present in weeks) have been

reported and known for years (3,4). While definitive diagnosis is only made possible by biopsy or autopsy, 2018. CDC criteria recognize probable diagnosis (positive clinical features combined with positive RT-QuIC in CSF/other tissues or typical EEG with triphasic periodic sharp wave complexes, positive 14-3-3 CSF assay, brain MRI with high signal in caudate/putamen, or two cortical regions visible on DWI/FLAIR) and possible CJD diagnosis (clinical features + duration of disease less than 2 years + alternative diagnosis excluded) (5). If not diagnosed at right time it can often end fatally before a final diagnosis is met. It is important to exclude potentially treatable causes. We present an atypical case of an sCJD which struck us by surprise, as the patient initially complained only of diplopia, and balance issues, with no complaints concerning memory or movement disorders.

Case report

A 57-year-old woman, with ulcerative colitis in the past medical history, was referred to our emergency department by her general practitioner for evaluation of a 2-week history of gait unsteadiness. She complained of progressive stance and gait instability along with trunkal and limb ataxia. She also reported a visual disorder that she described as a form of oscillopsia (her vision shimmered, unable to focus), with general complaints of anorexia and unintentional weight loss. During the initial interview in the neurological emergency infirmary, the patient did not exhibit obvious cognitive dysfunction, her neurological examination revealed subtle dysarthria, diplopia with left gaze, wide-based ataxic gait with occasional small steps, sinistropulsion in Romberg position, and ataxia of the limbs, predominantly of the left arm. The brain CT performed in the emergency department did not show evidence of any significant lesions. Initially hospitalized as an ataxia of unknown cause the diagnostic workup went on to exclude more common disorders of coordination and vertigo. Upon the more detailed taking of medical history, the patient was revealed to have subtle difficulties in reconstructing details from her life. Montreal Cognitive Assessment (MoCA testing) was done and revealed a surprising 21/30 result. Afterward, detailed medical history of the patient was taken from the patient family members who stated that she has had a periodically reduced attention span in the last couple of months, they also reported impairment of short-term memory and language difficulties in the form of subtle occasional dysarthria and comprehension difficulties. They also noticed certain behavioral changes a couple of months before, she became overprotective over her grandchildren, bad-tempered, and withdrawn. Her family denied myoclonic jerks, tremors, and other involuntary movements, or psychotic features. There was no history of major surgery or blood transfusion, corneal transplantation, or traveling to the tropics and subtropical regions. Laboratory results including basic full blood count, metabolic panel, hepatitis B and C, human immunodeficiency virus, autoimmune diseases screen and tumor markers, vitamin B12 and folate acid, and thyroid hormone levels were unremarkable. Biochemical and cytological analysis of CSF was also unremarkable, bacterial culture and test for viral encephalitis (HSV, VZV, *morbilli, mumps*) from the CSF sample excluded infectious disease. On the fourth day of hospitalization brain MRI was performed and revealed slightly increased signal intensity from the head and body of n. caudatus on the left side on T2 and FLAIR sequences (images 1.-4.). Restricted diffusion in the DWI sequence was also observed in multiple cortical areas bilaterally, predominantly left frontal, parietal, and occipital cortex (images 5.-7.).

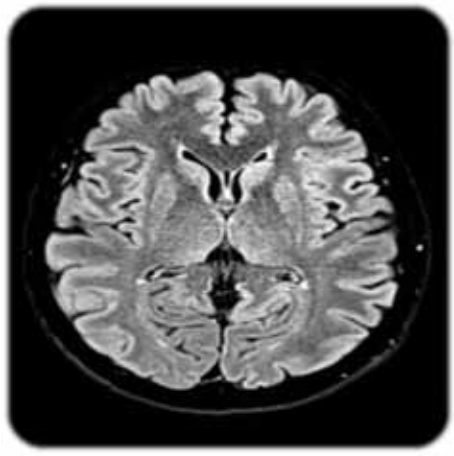

Fig. 1. FLAIR increase of signal of the head of left N. Caudatus

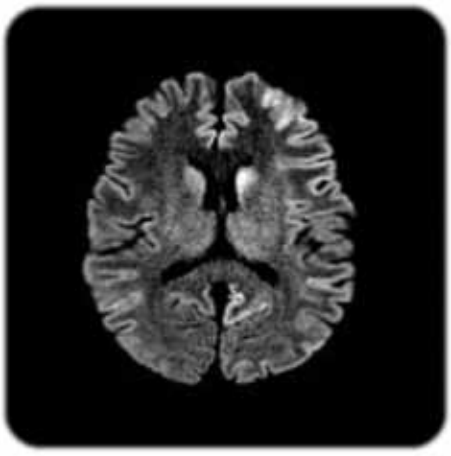

Fig. 2. DWI sequence N. Caudatus

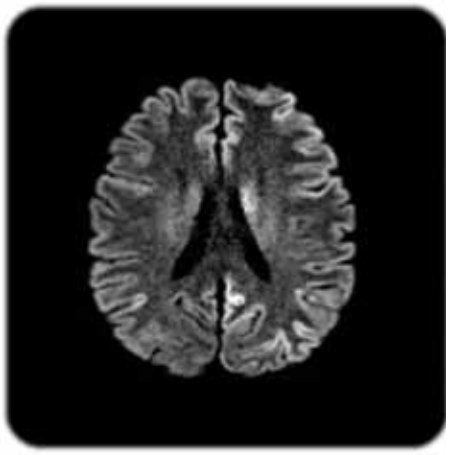

Fig. 3. DWI sequence N.Caudatus

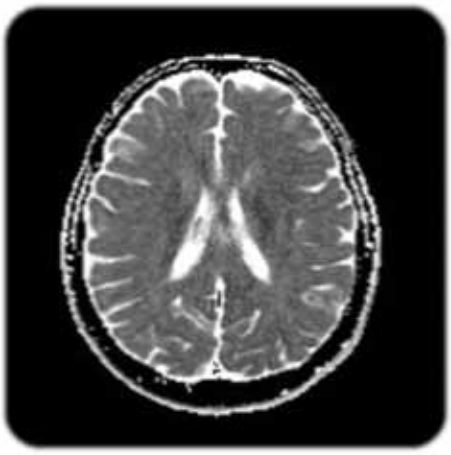

Fig. 4. ADC sequence N.Caudatus

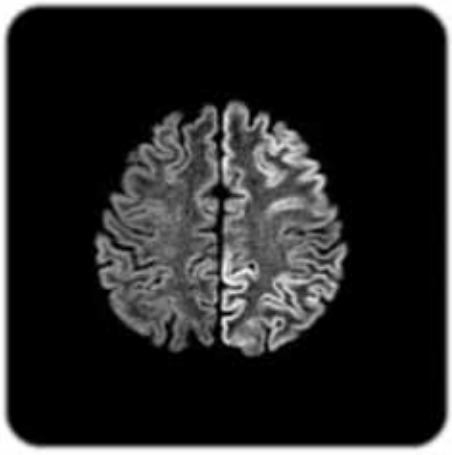

Fig. 5. DWI sequence frontal and parietal cortex with cortical ribboning.

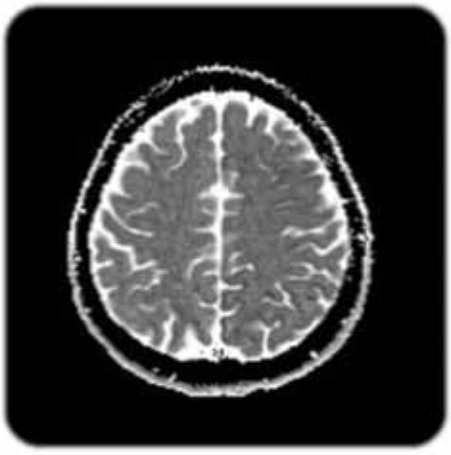

Fig. 6. ADC sequence frontal and parietal cortex signal change.

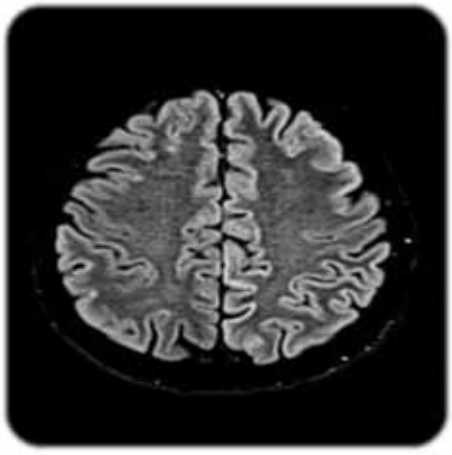

Fig. 7. FLAIR sequence frontal and parietal cortex

Thanks to an experienced neuroradiologist and a treatment team consisting of movement disorder specialists, and epilepsy specialists, a diagnosis of possible prion disease was made. Further confirming our suspicions EEG showed bilateral frontal slowing with typical intermittent triphasic waves, and delta activity, mostly left frontotemporal (image 9.-10.).

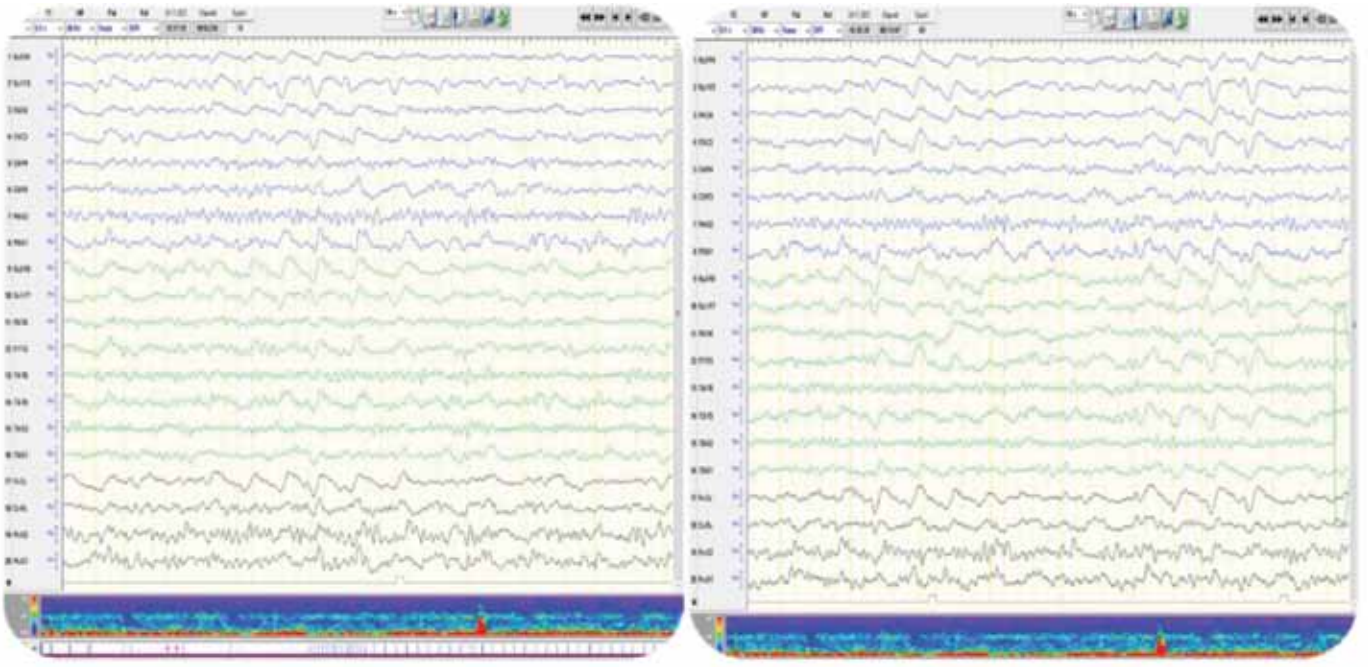

Fig. 9.-10. Typical triphasic waves are seen mostly in an area of the left frontotemporal cortex, and bifrontal cortex.

A CSF sample was sent to be confirmed with the *real-time quaking-induced conversion* (*RT-QuIC*) and it was positive. A diagnosis of probable sCJD was made with both the leading neurologist and the family members not being in favor of a confirmatory biopsy. The patient's family members were thoroughly informed about the disease process, the unfortunate lack of a cure, and further prognosis. Fulfilling the wishes of the patient and the patient's family members detailed information regarding the disease process was mercifully withheld from the patient. At the time of discharge from the hospital (13 days of hospitalization), the patient was slightly disorientated in time, but well-orientated in place and to a person with progressive moderate cognitive decline, besides those impairments, neurological examination was stationary in comparison with the first examination. 5 days after discharge from our Department, she was admitted to our Emergency Department because of exacerbation of her symptoms in the form of complete inability to walk, variable disorientation in time, space, to herself and persons around her, and a deterioration of other cognitive functions. She was complaining of blurred vision and worsening of prior visual disturbances and she was unable to follow simple verbal commands. Routine blood and urine tests were within normal limits. Chest X-Ray and brain CT were unremarkable. She was discharged from the hospital and sent to home treatment as per the wishes of the family. Arrangements were made for home care by the family members which was afterward escalated to hospice care. Four weeks later, she was readmitted to the emergency department because of a disturbance of consciousness. She presented in a state of akinetic mutism, with bilateral spontaneous horizontal nystagmus and rigor bilaterally, more marked on the left side. Blood test and chest X-Ray were normal, urine examination showed a urinary tract infection. Despite supportive and palliative treatment patient, unfortunately, expired three months after the onset of the symptoms. As per the wishes of the family autopsy of the patient was not performed.

CLÍNIC BARCELONA Hospital Universitari

Informe Parcial

Centre de Diagnòstic Biomèdic

Nombre: [redacted]
Fecha Nacimiento: [redacted]
s/Referencia:
Nº Petición CDB: [redacted]
Fecha Recepción: [redacted]
Fecha Finalización: [redacted]

ALTRES (NOMES PER LABORATORIS)

	RESULTADO	UNIDADES	VALOR REFERENCIA
INMUNOLOGIA CLINICA			
INMUNONEUROLOGIA			
Detección de proteína priónica para el diagnóstico de la Enfermedad de Creutzfeldt-Jakob, LCR	Positive		

Interpretación

SAMPLE: Cerebrospinal fluid

REASON FOR CONSULTATION: Suspected Creutzfeldt-Jacob disease.

METHODOLOGY: Real-time quaking-induced prion protein conversion (RT-QuIC).

According to McGuire LI *et al* (2012) this tecnique showed a sensitivity and specificity of 89% and ~100%, for the diagnosis of sporadic Cretzfeldt-Jakob.

RESULT: POSITIVE

INTERPRETATION / CONCLUSION: The positive test, on a compatible clinical context, is highly suggestive of Creutzfeldt-Jakob disease.

If you are interested in doing genetic studies of the prion protein gene to determine the polymorphism of codon 129 or screening for mutations, please send us 20 ml of fresh blood (no need to refrigerate) in tubes containing citrate or EDTA as an anticoagulant and 5 ml of serum as well as a copy of informed consent for genetic study.

TECHNICAL LIMITATIONS: This interpretation is subject to compliance with the preanalytical conditions set by the CDB.

Assay certified by:

Fig. 11. Positive RTQuIC which was analyzed at an partner facility.

Discussion

Being that our patient initially presented with symptoms of ataxia, diplopia, and slight dysarthria our initial suspicion was of cerebrovascular disease of posterior circulation, metabolic, toxic, or autoimmune encephalopathy. Subtle cognitive changes were masked by the high education of our patient who continued to read and solve newspaper quizzes during an initial couple of days of hospitalization. Only through detailed history taking, and analysis did we find initial neuropsychiatric symptoms which were corroborated by family members' statements, and confirmed with a low MoCA score. Standard and extended biochemical, cytological, and infectious analysis of both serum and CSF was normal, excluding meningitis, encephalitis, and toxic and metabolic encephalopathy. At this stage, a high level of suspicion is needed to guide a clinician to the right diagnosis as a brain MRI was reported positive for prion disease thanks to the experience and coordination of our neuroradiologist and neurological team. Medical history and neurological status combined with brain MRI data, and then EEG data further solidified probable sCJD diagnosis. RT-QuIC results from CSF confirmed the diagnosis as probable sCJD excluding other differential diagnoses. With only supportive treatment the patient, unfortunately, expired 3 months after the onset of symptoms.

Symptoms of sCJD are numerous and present a highly recognizable syndrome if the clinician is wary of possible prion disease in a population. But these symptoms are hardly specific for CJD. Different types of CJD present different clinical pictures. Recent use of genetic sequencing and high-end diagnostic workout has enabled detailed identification of different types of sCJD depending on polymorphism of the prion gene PRNP at the codon 129 (either methionine M or valine V) and prion molecule type (type 1 or 2). These subtypes differ in the initial neuroanatomical location of prion accumulation and with its initial symptoms, while ancillary testing using MRI, EEG, and CSF tests are mostly positive in similar percantages. Frequent types are: MM1/MV1 (median age 68, median disease duration 4 months) is the most common form with diffuse cortical and thalamic involvement causing early dementia, ataxia, myoclonus, and visual disturbance, MV2 (median age 65, median disease duration 17 months) with slowly progressive ataxia, dementia, and extrapyramidal symptoms, VV2 (median age 64, median disease duration 6.5 months) severe ataxia, late dementia, early severe cerebellum involvement. Rare types are: MM2 affecting thalamus (median age 52, median disease duration 16 months) causes insomnia and agitation early on, followed by ataxia and cognitive changes, MM2 cortical (median age 64, median disease duration 16) causing progressive dementia which lasts for months, VV1 (median age 44, median disease duration 21) younger patients affected with slowly progressive dementia, ataxia, and extrapyramidal symptoms, MM1 with amyloid plaques (median age 58, median disease duration 22) slower variant of typical MM1 only discernable by typical amyloid PrP plaques on biopsy or autopsy. Hereditary CJD is distinguished by positive family history thanks to autosomal dominant mutations in the PRNP gene, younger age of presentation, with Gerstmann-Straussler-Scheinkerand syndrome, and Fatal Familial Insomnia biomarkers and MRI is inconclusive. Iatrogenic CJD requires a history of transplantation or medical device implantation, while variant CJD needs a direct animal-to-human transmission (typical MRI pulvinar signal intensity, EEG, CSF, and RtQuIC inconclusive) (6). Being that sCJD is a diagnosis with no active treatment and therefore terminal it is first necessary to exclude potentially treatable causes of ataxia and/or fast-progressing dementia. Usually, the most similar clinical presentation to sCJD with its subacute cognitive impairment, psychiatric symptoms, ataxia, movement disorders, and seizures is attributed to autoimmune and paraneoplastic encephalitis. Brain MRI changes are similar with some characteristic differences such as typical predisposition for limbic localization of

FLAIR/T2W hyperintensity, subcortical hyperintensity, and cerebellar involvement usually not seen in sCJD. Positive autoantibodies and cancer biochemical markers with radiological confirmation of a neoplasm alongside a positive medical history of weight loss and previous nonspecific symptoms (fever, fatigue) steer the clinical diagnosis in this direction. Infective meningoencephalitis besides its symptoms of encephalopathy is often followed by high fever, headache, and neck stiffness. What differentiates this illness from sCJD is its positive epidemiology, serum and CSF immune markers (elevated protein, leukocyte count, change in glucose), positive bacterial culture, positive PCR (for HSV, EBV, JC, West Nile virus, etc.), more pronounced memory loss, and a tendency for seizure with mesial temporal signal changes in MRI in case of viral encephalitis. JC granule cell neuronopathy should be suspected when confronted with progressive ataxia, and dysarthria in immunocompromised patients. Positive PCR for the JC virus, impressive cerebellar atrophy, and cerebellar signal changes make a distinction against sCJD. Protracted hypoglycemia in diabetic patients or patients with hypermetabolic glucose consumption on rare occasions produces a similar clinical picture with seizures, movement disorders, consciousness disorders, and similar brain MRI findings affecting cortical areas and basal ganglia. Nonketotic hyperglycemia-induced hemichorea as a differential diagnosis presents contralateral basal ganglia T1 hyperintensity with absent T2, FLAIR, or DWI changes. Biochemical analysis and analysis of preceding events usually resolve both issues. Mimicking brain MRI changes similar to sCJD have been reported in patients coming out of status epilepticus, however, their transient nature is confirmed with a control MRI scan discerning them from sCJD. Patients with severe hepatic disorder and hyperammonemia provide a similar pallete of symptoms and MRI signal changes but are differentiated from sCJD by the severe metabolic state of the patient usually responding well to the treatment of hyperammonemia. Inadvertent swift recovery of hypoosmolar or hyperosmolar states with its hemiparesis, pseudobulbar palsy, consciousness disorders, and bilateral FLAIR/T2 hyperintensity in basal ganglia is similar to sCJD while medical history, previous electrolyte disbalance, rapid symptom onset, and lack of DWI hyperintensity makes a distinction from sCJD. Wilson disease and Wernicke encephalopathy are easily treatable subacute encephalopathies with movement disorders, ataxia, and cognitive changes different from sCJD by limited cortical involvement and more pronounced basal ganglia involvement on brain MRI with readily recognizable copper, and thiamin deficiency in biochemical analysis. They should be among the first suspects excluded as they are readily treatable, and respond favorably to acute treatment (7). When presented with progressive dementia, sCJD is often mistaken for rapid Alzheimer's disease, and while AD can present with myoclonus, positive EEG and 14-3-3 it has substantial temporal and hippocampal cortical atrophy detected on MRI (cortical atrophy is minimal in sCJD) with sCJD and ADs incident rate diverging as age progresses. Other dementias such as Lewy body dementia, and frontotemporal dementia together with atypical Parkinson's disease (such as progressive supranuclear palsy, and corticobasal degeneration) besides typical and readily recognizable symptoms are slower progressing than sCJD with life spans after diagnosis measured in years compared to months (8,9). The only diagnostic method providing a definitive diagnosis of CJD is a biopsy of the affected brain tissue or tonsils (in vCJD). Paradoxically the biopsy of CJD patients has reported low positive diagnostic rates, with low changes in treatment protocols questioning its utility. Dangers of proceeding with biopsy due to high infectiousness are nowadays reserved for resolving high suspicions of a treatable disease or only in the last ditch effort of diagnosing atypical cases of CJD. Confirmatory biopsies or autopsies are nowadays omitted in favor of noninvasive diagnostic tests with high specificity such as RTQuIC (10). Extended analysis of blood serum, and CSF are used to exclude sCJD mimics. Brain CT is usually normal, only in late stages presenting with nonspecific cortical atrophy (1). Diagnostics that have the highest yield in terms of positive diagnostic outcome are MRI (especially DWI, FLAIR/T2W sequence), EEG, and RT-QuIC from CSF. Technological solutions of brain MRI have proven themselves to be an excellent primary method in diagnosing CJD. The sensitivity of an MRI in diagnosing CJD currently exceeds even those of CSF biomarkers such as 14-3-3 proteins, neuron-specific enolase, and T-tau (11) Sensitivity of brain MRI in detecting sCJD is reported to be 91% with reported 95% specificity. Unfortunately, routine MRI is normal in as much as 21% of patients with early sCJD, with later visible changes presented with advancing stages of the disease (12,13). The most sensitive sequence to identify characteristic changes is diffusion-weighted imaging (e.g. b=1000) which demonstrates an increased signal, that is more conspicuous than either T2/FLAIR changes or ADC abnormalities. ADC is variable and depends on timing. In the early phase, low values may be seen before marked changes in DWI or visible FLAIR changes, and at a late phase pseudonormalised or facilitated and associated with atrophy. T2-FLAIR hyperintensity is more subtle than DWI changes and may be absent early in the course of the disease (7,14-16). DWI sequence is especially useful with uncooperative patients with as little as 30 seconds needed for image acquisition. Vacuolation of brain tissue restricting water molecule diffusion presents a positive image even in patients with a mild clinical presentation with negative EEG, and CSF biomarkers (12). Typical MRI presentations of CJD include cortical ribboning (hyperintense signal in the cerebral cortex), a hyperintense signal in the caput of nuclei caudate, putamen, and thalamus (double hockey sign, and pulvinar sign more specific for vCJD) (13). SCJD imaging is remarkable for the absence of signal change in the cerebellum besides atrophy even though a high burden of

cerebellar symptoms would suggest otherwise (7). Furthermore, sCJD lesions have no gadolinium uptake (14-16). EEG presents as another highly accessible diagnostic method with typical triphasic sharp wave complexes and less specific but equally important burst wave suppression patterns. Characteristic triphasic sharp wave complexes in EEG are present in 67% of patients with sCJD, problematic aspect is that they may not develop until late in the disease course (usually 12 weeks after symptom onset) and may disappear with disease progression. Repetitive EEG recording raises the sensitivity to 90% and specificity to 86% (12,17). Characteristic symptoms of fast-progressing dementia, myoclonic jerks, and positive triphasic sharp wave EEG activity can be absent in at least 25% of sCJD patients (12). A recent advancement in biomarker diagnostics in the form of real-time quacking-induced conversion (RT-QuIC) analysis of CSF has an astonishing sensitivity of 92% and specificity of 100%. It uses the ability of the misfolded prion protein from CSF to change the confrontation of normal PrP into a misfolded form which is then monitored using a fluorescent dye. The properties of this technique have made it essential in the modern diagnostics of CJD. Guidelines acknowledge patients with neuropsychiatric symptoms, and positive RT-QuIC as probable sCJD without the need for other tests to be positive (18,19). RT-QuIC as a method is imperfect in its cost, and availability. In case of inability to perform RT-QuIC other more traditional CSF biomarkers are also more than useful. Among them Total (t)-tau has proven to be the best surrogate CSF marker with 91.3% sensitivity and 78.9% specificity, after which comes 14-3-3 (ELISA 85.4% sensitivity, 68.8% specificity; Western blot 78.9% sensitivity, and 66.1% specificity), and neurofilament light chain protein NfL (>95% sensitivity, but 43.1% specificity) (20). The quest for finding the definitive cure for CJD has been long and unfortunately unfruitful. Starting with amantadine with only observational studies speculating on its antiviral properties, no effect on disease progress was made with only scarce clinical improvement (21). The first randomized double-blind controlled study of a drug in CJD was conducted with flupirtine having a transient beneficial effect on cognitive functions with no effect on survival time (21,22). Initially tried as compassionate treatment in observational studies quinacrine with its ambiguous results (unsubstantial clinical improvement with no effect on survival time) was finally put to rest in another double-blind randomized controlled study which found no effect of quinacrine on the survival of patients with sCJD (21,23). As is with quinacrine initially positive experimental outcomes and hypotheses in observational studies of doxycycline proved not applicable in a randomized controlled study (21). It is only with the intrathecal application of pentosan polysulphate that substantial improvement in survival time was found but only in patients with vCJD (21). Research is ongoing with the first experimental treatment of CJD patients with anti-PrPc monoclonal antibody (PRN100) reported (24). Alternative to animal studies human cerebral organoids are proposed as a novel model for screening future CJD drugs potentially accelerating the process (25). Many of the aforementioned drugs showed their hypothetical positive effect in the in vitro or experimental animal studies with early phases of CJD. These states are hardly translatable to the current state of human CJD cases. However, proof that RCT is possible in this rare disease, and more pronounced public consciousness of this disease together with guided international surveillance strategies provide reasons to be hopeful for the future. Correct diagnosis of CJD is important even though there are still no specific ways of treating this disease. The patient and their family/caregiver(s) must be spared the frustration of uncertainty and inadequate therapy. Knowledgeable, and compassionate clinicians, proper informing of the patient, family members/caregivers, and guidance in the process of neuropalliative care can give enough time to accept, and prepare for the inevitable end, and with correct symptomatic treatment temporally alleviate discomfort (26).

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