



Primer on Human Prion Disease

Your patient came to the UCSF Memory and Aging Center website looking for information about Jakob-Creutzfeldt disease (CJD), other prion diseases or rapidly progressive dementia (RPD). If your patient exhibits the features of an RPD, here are some helpful points we like to consider when narrowing the diagnosis.

Human prion diseases occur in sporadic, genetic and acquired forms. Prion diseases have an incidence (and death) rate of about 1 case per million people each year worldwide and typically affect people between 50 and 75 years of age, although younger and older cases also occur. The most common form of prion disease, sporadic Jakob-Creutzfeldt disease (sCJD), accounts for about 85% of prion diseases. Approximately 15% are inherited and associated with coding mutations in the *PRNP* gene, and less than 1% are acquired (i.e., infectious or transmitted).

The disease course of CJD is highly variable and may mimic many other neurological disorders. Affected individuals often experience behavioral changes, changes in cognition (e.g., confusion, problems with memory, language, processing of vision) and/or incoordination. This is often followed by a rapidly progressive dementia associated with progressive cerebellar ataxia, visual symptoms (e.g., double vision, visual misperception and distortion), myoclonus and other pyramidal/extrapyramidal features. People with prion disease also may experience insomnia, depression or unusual sensations. As many as 1/3 of patients have early constitutional complaints, which can include headache, general malaise and sometimes a dry cough.

As the disease progresses patients may become blind, mute and unable to control their limbs and ultimately succumb to organ failure or aspiration pneumonia. In most cases, death occurs within several months of symptom onset. Prion diseases currently are invariably fatal, and there is no proven treatment or prophylaxis, although treatment trials are ongoing and this is an active area of research.

Recommended RPD Work Up

Physical exam and patient history. Because the first symptoms of CJD are sometimes constitutional, identifying the actual date of onset may require some probing. An assessment of the patient's ability to complete activities of daily living helps quantify disease progression. Ask about any family history of neurological or psychiatric disease (relatives may have been misdiagnosed; many patients with genetic prion disease are mistaken for other neurological or psychiatric disorders, including Alzheimer's, Parkinson's disease or atypical parkinsonian dementias). Medical and travel history may help assess risk of acquired CJD.

Blood work. The following labs will cover a broad groundwork for an *initial* work-up: CBC, chemistry panel (including Ca, Mg and P), LFTs, RPR, rheumatology screen (ESR, ANA, RF, CRP, C-ANCA and P-ANCA), thyroid

function, B12, homocysteine, anti-thyroglobulin and anti-thyroperoxidase antibodies, HIV, Lyme and paraneoplastic antibodies. We recommend testing blood for genetic forms of prion disease in all patients with suspected CJD, particularly those with a family history of dementia or a cerebellar or parkinsonian disorder. In more than 60% of patients identified as having genetic prion disease, there is no known family history of prion disease. See the "Differential Diagnosis" section for additional suggested testing.

Urinalysis. UA and cultures should be sent to rule out infection. Collect 24-hour urine for heavy metal screen including: arsenic, lead, mercury, copper, aluminum and bismuth, with history of exposure.

MRI. This is the *single most helpful test* you can do to diagnose CJD. Order axial and coronal T1, T2, DWI (and ADC map) and FLAIR sequences. To rule out other conditions at least one MRI should be done with and without contrast.

EEG. In most people with CJD, the EEG will show a nonspecific slowing of activity which occurs in many forms of dementia. About 65% of patients with sCJD will show characteristic Periodic Sharp Wave Complexes (PSWCs) about once every second, but often not until late in the disease course. These changes are also not specific to CJD; they can occur in hepatic encephalopathy, Hashimoto's

encephalopathy and late stages of other neurodegenerative diseases such as Alzheimer's disease (AD) and Dementia with Lewy Bodies (DLB).

CSF (LP). The utility of the 14-3-3 protein in the diagnosis of CJD has been widely debated. While it remains a key feature of the WHO probable CJD criteria, only about half of the patients diagnosed with CJD at UCSF have had an elevated 14-3-3 protein and about 1/3 of patients referred to UCSF with elevated 14-3-3 have another diagnosis.

We have found that other CSF proteins, neuron-specific enolase (NSE) and total tau (t-tau), may be somewhat better than 14-3-3 for diagnosing CJD, but none are currently as helpful as a brain MRI. In some circumstances, these proteins may be helpful in supporting a CJD diagnosis, but do not use them in isolation to make a diagnosis, as they are probably merely markers of rapid neuronal injury.

We recommend testing for cell counts and differential, protein, glucose, IgG index, oligoclonal bands (OCBs) and VDRL, as well as total tau, A-beta, and 14-3-3 protein. Though not particularly specific to CJD, these proteins are reflective rapid neuronal injury or death.

CT. A CT of the chest, abdomen and pelvis with and without IV contrast can help rule out malignancy and paraneoplastic disorders.

Brain biopsy. With the utility of DWI MRI, we rarely do brain biopsies; however, a brain biopsy sometimes may help confirm CJD or another diagnosis. Brain biopsies, even in CJD, may not be diagnostic, as they do not always obtain tissue from the affected part of the brain.

Differential Diagnosis

A diagnosis of probable CJD requires an extensive exclusionary

work-up. The mnemonic device “**VITAMINS**” highlights other potential causes of rapidly progressive dementias:

Vascular Infectious

- Viral encephalitis, including herpes simplex virus
- HIV dementia
- Progressive multifocal leukoencephalopathy
- Subacute sclerosing panencephalitis (young adults)
- Fungal infections (immunosuppression [e.g., central nervous system (CNS) aspergillosis])
- Syphilis
- Lyme disease (rarely encephalopathy)
- Balamuthia
- Whipple's disease

Toxic-metabolic

- Endocrine abnormalities (thyroid disturbances, parathyroid abnormalities, adrenal diseases)
- Electrolyte abnormalities (including Ca, Mg, P)
- Vitamin deficiency (B12[cyanocobalamin], B1 [thiamine], niacin, folate [dementia rare])
- Uremia
- Wilson's disease
- Hepatic encephalopathy
- Porphyria
- Bismuth toxicity
- Metal (lithium, bismuth, lead, mercury, arsenic) toxicity

Autoimmune

- Hashimoto's encephalopathy (HE)
- Paraneoplastic (autoimmune) limbic encephalopathy (PLE)
- Nonparaneoplastic autoimmune (e.g., anti-voltage-gated potassium channel [VGKC] antibodies mediated)
- Lupus cerebritis
- Other CNS vasculitides
- Sarcoid

Metastases/neoplasm

- Non-autoimmune paraneoplastic conditions
- Metastases to CNS
- Primary CNS lymphoma (PCNSL)
- Intravascular lymphoma
- Lymphomatoid granulomatosis
- Gliomatosis cerebri

Iatrogenic

Neurodegenerative

- Prion disease
- AD

- DLB
- FTD
- CBD
- Progressive supranuclear palsy (PSP)

Systemic

- Sarcoid
- Mitochondrial disease (e.g., MELAS)

Diagnostic Criteria

sCJD – Criteria for Definite Sporadic Jakob-Creutzfeldt Disease (WHO 1998)

1. Diagnosed by standard neuropathological techniques
2. *AND/OR* immunocytochemically
3. *AND/OR* Western blot confirmed protease-resistant prion protein (PrP)
4. *AND/OR* presence of scrapie-associated fibrils

sCJD – Criteria for Probable Sporadic Jakob-Creutzfeldt Disease (UCSF 2007)

1. Rapid cognitive decline
2. At least 2 of the following 6 symptoms:
 1. Myoclonus
 2. Pyramidal/extra pyramidal
 3. Visual
 4. Cerebellar
 5. Akinetic mutism
 6. Other focal higher cortical sign (e.g., neglect, aphasia, apraxia, acalculia)
3. Positive EEG (periodic epileptiform discharges) or positive MRI (either sub-cortical hyperintensity or cortical gyral hyperintensity [cortical ribboning] on DWI and preferably restricted diffusion on ADC map) *OR* both
4. Routine investigations do not suggest an alternative diagnosis.

sCJD – Criteria for Probable Sporadic Jakob-Creutzfeldt Disease (WHO 1998)

1. Progressive dementia
2. At least 2 of the following 4 symptoms:
 1. Myoclonus
 2. Pyramidal/extrapyraxidal
 3. Visual or cerebellar

4. Akinetic mutism
3. *AND* a positive EEG (periodic epileptiform discharges) *AND/OR* positive 14-3-3 protein result and < 2 year disease duration
4. Routine investigations do not suggest an alternative diagnosis.

sCJD – Criteria for Possible Sporadic Jakob-Creutzfeldt Disease (WHO 1998)

1. Progressive dementia
2. At least 2 of the following 4 symptoms:
 1. Myoclonus
 2. Pyramidal/extrapyramidal
 3. Visual or cerebellar
 4. Akinetic mutism
3. Without a supportive EEG

gCJD – Criteria for Genetic Jakob-Creutzfeldt Disease

1. Identified *PRNP* mutation
2. *OR* symptomatic with positive FMH

vCJD – Criteria for Definite Variant Jakob-Creutzfeldt Disease (UK DoH 2003)

1. Progressive neuropsychiatric disorder
2. Neuropathological confirmation of the disease showing spongiform change and extensive PrP^C deposition with florid plaques throughout the cerebrum and cerebellum

vCJD – Criteria for Probable Variant Jakob-Creutzfeldt Disease

There are two sets of criteria for patients with probable vCJD.

Criteria A.

1. Progressive neuropsychiatric disorder for more than 6 months
2. Routine investigations do not suggest an alternative diagnosis
3. At least 4 of the following 5 symptoms:
 1. Early psychiatric symptoms (depression, anxiety, apathy withdrawal, delusions)

2. Persistent painful sensory symptoms (including both frank pain and/or unpleasant dysaesthesia)
3. Ataxia
4. Myoclonus, chorea or dystonia
5. Dementia
4. EEG does not show the typical appearances of sporadic CJD *OR* no EEG has been performed
5. Symmetrical high signal in the posterior thalamus on a MRI brain scan (Zeidler *et al* 2000)
6. No history of potential iatrogenic exposure

Criteria B.

1. Progressive neuropsychiatric disorder for a period of longer than 6 months
2. Routine investigations do not support an alternative diagnosis
3. No history of potential iatrogenic exposure
4. Positive tonsil biopsy, which is positive for PrP-res

vCJD – Criteria for Possible Variant Jakob-Creutzfeldt Disease

1. Progressive neuropsychiatric disorder for more than 6 months
2. Routine investigations do not suggest an alternative diagnosis
3. No history of potential iatrogenic exposure
4. At least 4 of the following 5 symptoms:
 1. Early psychiatric symptoms (depression, anxiety, apathy withdrawal, delusions)
 2. Persistent painful sensory symptoms (including both frank pain and/or unpleasant dysaesthesia)
 3. Ataxia
 4. Myoclonus, chorea or dystonia
 5. Dementia
5. EEG does not show the typical appearance of sporadic CJD or no EEG has been performed

iCJD – Criteria for Iatrogenic Jakob-Creutzfeldt Disease CJD

1. Meets criteria for sCJD
2. Positive medical history of CJD exposure via contaminated surgical instruments (e.g., biopsy equipment), dura graft, or other substances (e.g., human cadaveric-derived growth hormone, corneal transplant)

Management of Symptoms

While there is no proven cure or treatment for CJD, many of the symptoms can be managed either pharmaceutically or behaviorally. Opiate drugs can help relieve pain if it occurs, and the drugs clonazepam and sodium valproate may help relieve myoclonus, although one paper showed valproic acid worsened prion activity *in vitro* (but not in a live murine model).

During later stages of the disease, changing the person's position frequently can help maintain comfort and prevent bedsores. A catheter can be used to drain urine if the patient cannot control bladder function, and intravenous fluids and artificial feeding also may be used. It is helpful to specifically note whether or not the patient can swallow or follow simple commands, as you may need to arrange for specialized help if either of these cannot be done.

Clinical Trials and Research

If you would like to refer your patient to clinical research, we are currently enrolling patients in two different CJD-related studies.

New Clinical Approaches to the Assessment of Rapidly Progressive Dementias and Neurologic Conditions.

The primary goal of this study is to

develop and test methods for differentiating CJD and other prion diseases from other diseases and to learn how to diagnose CJD as early as possible. A secondary goal of this study is to learn more about how CJD and other rapid neurological conditions progress by studying these diseases in each patient over time.

Because CJD is a rare condition and it is very rapidly progressive, diagnosis of the disease often is made very late in the illness. If any future treatments for CJD are to be successful, they likely will need to be given to patients as early as possible, before the disease progresses too far. It is therefore important that we learn how to make an accurate diagnosis earlier.

For more information, contact Aissa Haman, MD: (415) 476-2905, ahaman@memory.ucsf.edu or Amy Kuo, RN: (415) 476-2907, akuo@memory.ucsf.edu.

Novel Therapeutics for Prion Diseases: A Randomized, Double-Blinded, Placebo-Controlled Study of the Efficacy of Quinacrine in the Treatment of Sporadic Jakob-Creutzfeldt disease. The goal of the Quinacrine Study is to determine the efficacy of quinacrine on survival in sporadic CJD (sCJD). This will be accomplished by bringing approximately 60 patients with probable or definite sCJD to UCSF for treatment study of quinacrine. Each patient will have a 50:50 chance of being placed on quinacrine or placebo upon study enrollment; however, all patients will be offered quinacrine after two months. Participants will come to UCSF for initial evaluation, potential study enrollment and, if possible, return to UCSF for follow-up at 2, 6 and 12 months.

For more information, contact Benjamin Raudabaugh: (415) 476-0670, braudabaugh@memory.ucsf.edu.

Transmissibility

Prions, the causative infectious proteins, are resistant to conventional chemical and physical sterilization and decontamination methods. They can usually be denatured or hydrolyzed, however, by soaking contaminated instruments in 1N sodium hydroxide for an hour or more and then autoclaving them in distilled water at 132-134 °C for at least an hour. It can be even more difficult to inactivate prions that have come into contact with materials such as metal or glass; when feasible, these instruments should be destroyed.

Tissue infectivity. The CNS tissues, specifically brain, dura mater, spinal cord and eye are highly infectious. In vCJD, lymphoreticular tissues are also highly infectious. Cerebrospinal fluid (CSF) and several organs outside the CNS (lung, liver, kidney, spleen and placenta) are considered less infectious but should still be treated with caution.

Only vCJD has been shown to be transmissible by blood transfusion from human to human. Although transmission from blood in other human prion diseases (not vCJD) has not been shown, there is a theoretical risk; therefore, any exposure with confirmed or suspected prion disease (or with a relative with CJD) must be considered exposure to prion disease.

It is not clear how cautious one needs to be in performing non-neurosurgical invasive procedures on patients with prion disease. Most medical centers treat such procedures and equipment with universal precautions. At our center, due to the high number of patients seen with prion disease, we are more cautious with invasive medical procedures.

When working or caring for patients with prion disease, casual and even intimate contact is not considered a risk factor. When dealing with bodily fluids and excretions, such as blood,

urine or feces, we recommend universal precautions (disposable gloves and disposing of material that comes in contact with such fluids).

Route of exposure. Human prion diseases are not known to spread by social contact, but transmission can occur during invasive medical interventions, exposure to infected human cadaveric-derived pituitary hormones, dural and cornea grafts, and contaminated neurosurgical instruments.

While there is no evidence of occupational transmission of CJD to healthcare workers, it is prudent to be cautious. The highest potential risk is from transcutaneous exposure to high infectivity tissues (CNS) through needle-sticks, puncture wounds, “sharps” injuries, or contamination of broken skin. Exposure by splashing of the mucous membranes (notably the conjunctiva) must also be avoided. Healthcare personnel who work with patients with confirmed or suspected prion disease, or with their tissues, should be appropriately informed about the nature of the hazard and relevant safety procedures.

If you experience a needle-stick or laceration:

1. Wash the affected area with 1N sodium hydroxide solution (household bleach) for 2-3 minutes.
2. Rinse well afterwards with soap and water to neutralize the base.
 - Sodium hydroxide is caustic but relatively slow-acting at room temperature and can be removed from skin or clothing by thorough rinsing with water for 15-30 minutes.
 - **DO NOT** use sodium hydroxide or bleach in eyes or mouth, or on any other mucous membrane. For a splash to the eye or mucous membrane exposure, rinse well with saline or tap water.

3. Cover wound with waterproof dressing to prevent secondary contamination.
4. Report your exposure.

For more information. Please see the

- *UCSF Infection Control Policies and Procedures for Patients with Suspected or Confirmed Human Prion Disease* at http://infectioncontrol.ucsfmedicalcenter.org/HTML/ICMANUAL/Sec4-11_Human_Prion_Disease_2005.pdf or the
- *WHO Infection Control Guidelines for Transmissible Spongiform Encephalopathies* at <http://www.who.int/csr/resources/publications/bse/whocdscsraph2003.pdf>.

Contact Us

If you would like a consult or to refer your patient to our clinic, please contact Dr. Michael Geschwind at mgeschwind@memory.ucsf.edu or call the RPD Clinic Coordinator at (415) 476-0670.

Fax medical records to the attention of Dr. Michael Geschwind at (415) 476-2921.

Mail copies of the actual MRI films, preferably on CD, to:

Attention: Dr. Michael Geschwind
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For more detailed information on anything you have read here, please visit us online at memory.ucsf.edu/cjd.