Grand Rounds

Familial Creutzfeldt-Jakob Disease: A Neuropsychological Case Study

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The spectrum of neuropsychological features of familial Creutzfeldt-Jakob disease (CJD) have seldom been reported, possibly because of (a) the rarity of this hereditary form of prion disease; (b) frequent delays in diagnosis, and; (c) the typically rapid demise of the patient, which affords little opportunity for comprehensive testing or serial analysis. Here we describe the neurobehavioral characteristics of a 48-year-old right-handed male (JD) who presented with complaints of poor depth perception, unsteady gait, and unusual sensory experiences in his face and neck. JD was followed serially over the final 4 months of his 5-month illness. Immediately following hospital admission, he underwent a neuropsychological evaluation that revealed moderate to severe impairment of delayed (30-minute) verbal memory, tactual performance in his right hand, and word-finding ability. In contrast, other abilities that are commonly classified within the verbal, visuospatial, and memory domains showed minimal or no compromise. Parallel studies of electroencephalographic activity revealed diffuse slowing and, later, 1-Hz rhythmical discharges over the left hemisphere, and mild prominence of the lateral ventricles and cerebral sulci on magnetic resonance imaging. Autopsy revealed spongiform changes and reactive astrocytosis, and genetic testing demonstrated a codon 200 mutation in the prion protein gene. These findings indicate that CJD can result in clinical manifestations compatible with multifocal asymmetric cerebral involvement before more diffuse neurodegeneration ensues, providing a strong impetus for the study of additional cases. This long-term understanding can help to determine whether

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Creutzfeldt-Jakob disease (CJD) is a rare and fatal neurodegenerative condition caused by a proteinaceous infectious agent called a “prion” (Prusiner, 1982). A rapidly progressive and profound dementia, cerebellar ataxia, diffuse myoclonic jerks, and a characteristic electroencephalogram (EEG) pattern often characterize the disease. Although infrequent (prevalence is <1 in 1 million), CJD holds considerable interest for several reasons. First, CJD is a unique example of a transmissible dementia. It has reportedly spread from person to person by way of administration of human pituitary growth hormone; tonsil biopsy; surgical procedures employing contaminated instrument or materials, including corneal transplant, dural grafting, and implantation of depth electrodes; and by contamination during autopsy (Brown, 1984; Brown, Gajdusek, Gibbs, & Asher, 1987; Clinton & Roberts, 1992; Weller, 1989). Second, CJD is similar in many respects to bovine spongiform encephalopathy (“mad cow disease”), which has recently been a matter of great concern in Great Britain because of the unproven possibility of transmission to humans (Epstein & Brown, 1997). This disease has a presumably long asymptomatic period followed by a rapid, relentless course that results in death within 3 to 12 months after symptom onset. Treatment is, so far, uniformly ineffective. Third, the disease appears not to be caused by a conventional virus, but by an aberrant protein (the prion) capable of catalyzing the conversion of the naturally occurring nonpathogenic form of the protein into this pathogenic form. The precise mechanism underlying prion-induced neurodegeneration is unknown. In addition to CJD, there are several other prion-based neurodegenerative conditions, including Gerstmann–Straussler–Scheinker disease, fatal familial insomnia, and kuru (Brown, 1984; Brown, Preece, & Will, 1992; Prusiner, 1982). These conditions share a tendency for neuronal loss with astrocytic proliferation in the absence of inflammation, and the formation of membrane-bound tissue vacuoles (Adam, Crow, Duchen, Scaravilli, & Spokes, 1982). The resulting parenchymal rarefaction justifies the older term spongiform encephalopathy, by which these conditions are also known (Brown et al., 1992).

CJD occurs worldwide and is equally represented in males and females (Adams, Victor, & Ropper, 1997). The most common form of CJD is sporadic (nongenetic) in nature, occurring in approximately 85% of documented cases. A second form is transmitted (iatrogenic), accounting for a very small number of widely publicized cases. Studies suggest that the incubation period in these cases ranges from 18 months to 30 years (Brown et al., 1992). Familial CJD is the genetic form that accounts for about 15% of human prion diseases, with an incidence of about 1 per 10 million (Dearmond & Prusiner, 1997). First reported in 1924, familial CJD is caused by one of several inheritable mutations in the prion protein precursor gene (PRNP) located on the long arm of chromosome 20. These mutations have been identified with varying degrees of empirical support at codons 102, 117, 129, 178, 198, 200, and 210 (Clinton & Roberts, 1992; Jubelt & Miller, 1995), and each appear to be associated with a strong tendency for distinct clinical features (Chapman et al., 1993; Dearmond & Prusiner, 1997; McCarthy, Weber, & Berger, 1996). Additional mutational linkages are being discovered (e.g., Cochran et al., 1996; Mastroianni, Iannicola, Myers, DeArmond, & Prusiner, 1996). The average age of symptom onset is earlier in familial CJD (46 ± 7 years) than in the sporadic form (55 ± 8 years), and the illness runs its course more slowly in the latter (average 22 months vs. 8 months).

Clinical presentations of CJD show considerable diversity in agreement with the ob-
served variability in the underlying frequency and distribution of lesions. A common tetrad of symptoms is usually apparent, however, and these include rapidly progressive dementia, ataxia, myoclonus, and periodic sharp-wave complexes in the EEG. In many cases, a prodromal phase is characterized by the emergence of nonspecific symptoms that often fluctuate in severity and vary widely among patients. A wide variety of disturbances in visual perception and cerebellar function are common. Vegetative symptoms include disturbance of sleep and appetite, fatigue, and decreased libido. Neuropsychiatric symptoms sometimes include disturbances in behavior (e.g., poor judgment, aggression, social withdrawal), cognition (e.g., distractibility, confusion, forgetfulness, bradyphrenia), language (e.g., word-finding, paraphasic speech), and emotional functioning (e.g., depression, irritability, anxiety, fatigue, paranoia). Florid psychotic manifestations occur early in many instances (Will & Matthews, 1984). The expression of these psychiatric features early in the illness often complicates the diagnosis (Keshavan, Lishman, & Hughes, 1987).

The prodromal phase of CJD, when it occurs, may last for months, and is then followed by an abrupt and rapid decline in mental, motor, and, in some cases, sensory functioning. In other cases, the onset is marked by a steady and consistent progression of symptoms or stepwise deterioration. In a third group of patients, an initial period of rapid deterioration may level off to a more slowly progressive terminal phase. Regardless of the clinical course, several symptoms commonly emerge in the middle stage of the disease, and these include the characteristic EEG abnormality, myoclonus, and a variety of pyramidal and extrapyramidal abnormalities. Delusions and hallucinations are also common, and may be associated with episodes of confusion, disorientation, and delirium. The final outcome is characterized by severe myoclonus and global dementia that progress to coma and death. This invariably fatal disease usually runs its course within 1 year from onset of symptoms, with only 5 to 10% of patients surviving for more than 2 years (Maertens & Quindlen, 1991).

With few exceptions, published case studies of sporadic CJD describe various medical, neurological, and psychiatric features, yet provide relatively little information about neuropsychological aspects of the disease. One report described a 61-year-old college-educated man who had CJD and initially presented with a progressive aphasia characterized by fluent and articulate speech compromised by frequent phonemic paraphasias and word-finding difficulties (Mandell, Alexander, & Carpenter, 1989). In addition, the patient demonstrated impaired auditory comprehension, agraphia, acalculia, ideomotor apraxia, and right versus left confusion, while exhibiting relatively normal function of nonverbal skills. Eventually, the CJD-linked EEG abnormality emerged in conjunction with rapid and generalized deterioration of neurobehavioral function, leading to the realization that this was not the more common progressive (usually Wernicke’s) aphasia syndrome that occurs in a subset of patients with Alzheimer’s disease.

A different neuropsychological presentation in a 39-year-old man with early symptomatic CJD was reported by Bieliauskas and Fox (1987). This patient initially presented with a 1-year history of intermittent diplopia, fatigability, emotional lability, and forgetfulness. On examination, he had impaired attention and delayed (30-minute) recall on the Wechsler Memory Scale (WMS; Wechsler, 1945), as well as deficits in the areas of graphomotor function, reading comprehension, and writing. Finger-tapping speed, gnosia, and praxis were intact bilaterally. One month later, retesting revealed diminished functioning across all of the measured domains, with the exception of preserved motor speed in both hands and sentence production. The authors raised the question of whether fine motor performance might represent a relatively stable function in the early stage of CJD.
The present case study presents neuropsychological evaluation results obtained on the second day of hospitalization from a man who had the considerably rarer familial form of CJD, on which no previous reports seem to exist.

CASE REPORT

JD was a 42-year-old right-handed Caucasian male aircraft pilot and mechanic who initially presented in March 1997 to the Neurology Clinic as an outpatient with complaints of very slowly progressive attentional problems over the past year. No other abnormalities were reported during this period, and the results of the neurological examination were negative. His mental status exam revealed three out of four objects recalled after 4 minutes, and normal performance with respect to serial threes, confrontation naming, three-step commands, and spelling “WORLD” backwards.

Four weeks later, JD was admitted to our medical center with new (and different) complaints of generalized body aches and weakness; diminished depth perception; right facial numbness; paresthesiae over his eyelids; a hot sensation in the posterior portion of his neck; unsteady gait, with a tendency to fall to the right; and a decrease in handwriting quality. At this time, the patient stated that these symptoms had occurred intermittently over the past year, with increasing frequency over the 2 months preceding admission. He denied having any cognitive difficulties, though his wife reported that his memory had declined over the past year. She also reported that he had word-finding difficulties over the past 2 months.

![Figure 1](image-url)  
**FIGURE 1.** Pedigree of the patient’s family. Hatched squares indicate males with autopsy-verified Creutzfeldt-Jakob disease (CJD), and black squares indicate males with autopsy-verified CJD in which codon 200 PrP mutations have also been documented. Material suitable for genetic testing of any but these two cases is unavailable. The arrowhead identifies the patient reported here.
JD’s medical history included hepatitis C (in 1996), malaria (in 1968), intravenous drug use, and alcohol and cocaine dependence. He had been abstinent of cocaine for 3 years and of alcohol for 3 months. JD was initially unaware of the fact that four members of his extended family on his mother’s side had died of CJD, and this information did not become available to the medical team for several days following his admission. The mutational linkage had been identified on codon 200 in his family (Figure 1), which is by far the most common mutation associated with familial CJD (Goldgaber et al., 1989).

On the day of JD’s admission, the neurology team requested a computed tomography (CT) scan, EEG, and a neuropsychological evaluation to assist in diagnosis and treatment planning. The neurologic examination was unremarkable, except for dysmetria on

![FIGURE 2. Selected sections from JD’s computed tomography scan, arranged in a ventral (A) to dorsal (D) sequence. The study reveals mild dilatation of the lateral ventricles (best seen in panels B and C) and mild cortical atrophy (best seen in panels C and D).](image-url)
right finger-to-nose, decreased pin prick sensation on the right side of the face, and gait ataxia. All other sensory, motor, and reflex findings were within normal limits. The initial EEG revealed diffuse slowing in the left cerebral hemisphere with no epileptiform discharges. The CT scan revealed mild prominence of the lateral ventricles and cerebral sulci, but no other abnormalities were found (Figure 2).

The neuropsychological evaluation was conducted during the second day of JD’s hospitalization. He was alert and oriented in all domains. He was administered portions of the Halstead-Reitan Battery (Reitan & Wolfson, 1993) and selected subtests of the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) (Logical Memory and Visual Reproduction subscales). At the time of the evaluation, JD was mildly depressed and anxious, yet fully engaged in the examination process. He was markedly frustrated by occasional poor performance, and required substantial encouragement to continue. Myoclonic jerks were observed in his right upper extremity. Prior to completion of the examination, JD was informed of his strong familial history of CJD and its implications for his own prognosis. He became emotionally distraught and requested cancellation of further testing.

Neuropsychological Findings

JD’s quality of performance was highly variable across tests (see Table 1). Several of his measured abilities appeared to be completely intact, and these included fine motor speed and grip strength in the left hand, and retention of visuographic material after a half-hour delay. In general, performance using his left hand was superior to his right on several perceptual-motor tests, implicating the left hemisphere as a possible site of compromise. Motor speed and grip strength in the right hand showed evidence of marginal impairment. Other abilities also appeared be within the borderline to mildly impaired range of functioning. These included reading, visual scanning efficiency on the Trail Making Test, Part A, and graphomotor skill on the Rey Complex Figure (RCF). His ap-

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<tr>
<th>Instrument</th>
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<th>Impairment Range</th>
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<tr>
<td>Visual Reproduction II</td>
<td>32</td>
<td>Normal</td>
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proach to copying the RCF was very segmented, suggesting a failure to recognize the ge-
stalt or general configural aspects of the design.

JD’s performance on the Tactual Performance Test (TPT) involving the use of his left
hand was mildly impaired. Right-hand performance was much worse. It was very slow
and ineffective, and classified within the severe impairment range. Nonverbal concep-
tual reasoning on the Category Test showed evidence of mild impairment. Word-find-
ing, though not formally assessed, was observed to be problematic for the examinee. Al-
though JD’s recall on the Visual Reproduction subtest was within normal limits, he
displayed evidence of severely impaired encoding and storage processes for verbal prose
material (Logical Memory subtest). On immediate recall, he recounted 14 out of 50 de-
tails, which is about 65% of the expected amount of detail (Wechsler, 1987). However,
after 30 minutes, he had no recall of any of the prose material. Recognition testing using
a multiple-choice format (Gass, 1995) supported the conclusion of a prominent storage
deficit.

The results of the neuropsychological evaluation were judged to be consistent with bi-
lateral hemispheric compromise, left much worse than right, and posterior slightly more
affected than anterior. However, from a diagnostic standpoint, these findings were non-
specific in regard to the underlying neuropathology. JD’s initial denial of any cognitive
deficits stood in sharp contrast to his written responses on the Cognitive Difficulties
Scale (CDS; McNair & Kahn, 1983), which was administered just prior to the neuropsy-
chological examination. His responses on the CDS indicated an awareness of his limita-
tions in the areas of attention, concentration, and recent verbal memory.

Subsequent Clinical Course

JD’s condition deteriorated rapidly. One week after the neuropsychological evalua-
tion, his speech became mildly dysarthric and tangential in content. Word-finding prob-
lems became increasingly severe over the following 2 weeks. Fine finger movements and
alternating movements were substantially slower in both hands. Depression and sleep
disturbances intensified, and he was prescribed Elavil and Temazepam for their respec-
tive treatments. Symptomatic complaints soon included intermittent occipital head-
aches. A follow-up EEG revealed diffuse irregular slowing and rhythmical one per sec-
ond slow sharp transients, particularly over the left cerebral hemisphere. Intermittent
tonic-clonic seizures ensued. One month following his admission, JD displayed increas-
ing restlessness, lack of communication, and a new onset of visual hallucinations. He
then became mute. However, he was responsive to tactile stimulation and was able to
follow one-step commands for the 3-week period prior to becoming comatose. Death oc-
curred 2 1/2 months following his admission, and about 3 1/2 months after the obviously
progressive symptoms began.

Autopsy Results

The brain weighed 1,350 grams. Gross inspection of the brain revealed lateral ventric-
ular dilatation and mild diffuse atrophy, which was most prominent in the posterior pari-
etal lobes (Figure 3).

The substantia nigra was pale. Histological study demonstrated the commonly ob-
served triad of spongiform vacuolation, neuronal loss, and reactive astrocytosis through-
out the brain (Figure 4). The most severe changes were observed in the cerebral cortex,
claustrum, striatum, and dorsomedial nucleus of the thalamus. Neuronal loss was also
substantial in the anterior-lateral region of the occipital cortex. Milder changes were noted in the globus pallidus, hippocampus, substantia nigra, colliculi, and dentate nuclei. Histological staining also revealed diffuse demyelination and axonal loss. The cerebellum was relatively spared (not shown).

FIGURE 3. Photographs of the lateral (A) and medial (B) aspects of the left cerebral hemisphere and hemicerebellum, with attached brain stem. No abnormalities are apparent at this level of examination, other than mild gyral trophy.

FIGURE 4. Photomicrographs of a Bodian preparation of the right temporal cortex (A) and a hematoxylin-eosin preparation of the left frontal cortex (B). Both panels reveal clusters of semiconfluent spongiform changes consistent with the clinical diagnosis of a prion disorder. Panel B also shows hypertrophic reactive astrocytes (arrows) and a rare spared neuron (open arrow). Otherwise, the large pyramidal neurons characteristic of this region are conspicuously absent.
DISCUSSION

Familial CJD is an autosomal dominant neurodegenerative disease that is unique in that it is both hereditary and potentially transmissible. Because of its rarity, we were unable to find any previous studies that documented its neuropsychological characteristics. The familial form typically presents at an earlier age (46 ± 7 years) and often progresses to death at a slower rate (22 months) than the more common sporadic form of CJD (8 months). Nevertheless, the literature suggests that other clinical characteristics are very similar. The combination of rapid progressive dementia, myoclonus, ataxia, and periodic sharp-wave complexes in the EEG is almost pathognomonic of CJD in its various forms. On the other hand, regardless of whether CJD is hereditary, sporadic, or iatrogenic, the disease is characterized by a broad spectrum of phenotypes that have different clinical presentations and associated nonuniform regional distributions of neuropathology. The various subtypes include those with (a) prominent involvement of the occipital lobes with associated visual disturbances (Heidenhain variant), (b) cerebellar involvement with ataxia (Brownell & Oppenheimer, 1965), (c) striatal degeneration with extrapyramidal features (McCarthy et al., 1996), and (d) white matter demyelination with peripheral neuropathy (Antoine et al., 1996). Although there have been few published neuropsychological studies of CJD patients, it is reasonable to suspect that CJD cases will show diverse neurobehavioral patterns that may roughly correlate with the topographical distributions of the lesions, which is frequently not uniform nor symmetrical.

The present case of JD exemplifies the tendency of CJD to present initially with circumscribed neurobehavioral deficits that presumably reflect focal areas of cerebral compromise. JD’s most outstanding deficits (i.e., right-hand tactual performance and anterograde amnesia for verbal material) were consistent with the abnormal EEG activity in the left cerebral hemisphere. Other evaluative procedures, including the CT scan, failed to reveal the basis for the lateralized pathology. Previous case reports have included instances in which CJD initially presented with predominantly left hemisphere involvement and aphasic language disturbance (Mandell et al., 1989; Shuttleworth, Yates, & Paltan-Ortiz, 1985). The frequent absence of lateralized pathology on autopsy is consistent with the widespread destruction that results from the rapid progression of the disease. Consequently, a basis for early focal manifestations is seldom obtainable by macro- and microscopic postmortem examination after the disease has run its course. In fact, by the time JD had died, the disease had substantially affected both cerebral hemispheres (Figure 4).

The bulk of the clinical presentation and cognitive-behavioral profile in the present case did not resemble any of the widely recognized subtypes of CJD. However, the presence of significant memory impairment as an early symptom has been reported (Bieliauskas & Fox, 1987). Ultimately, after the rapid progression of the disease and deterioration of JD’s neurobehavioral status, the most affected neuroanatomic sites included the occipital cortex, dorsomedial thalamus, nigrostriatal pathway, midbrain, white matter, and, to a lesser extent, the cerebellum. Aside from the evidence from neuropsychological testing and the abnormal EEG implicating left hemisphere dysfunction, it is not known which specific areas of the brain were most seriously damaged in the earlier stages of the disease. Possible candidates, based on the neuropsychological evaluation results, include the left medial temporal area and dorsomedial thalamus, both of which play a critical role in memory storage. In any case, the weight of current evidence suggests that the specific sites of initial compromise in the brain vary substantially across affected individuals. The well-documented clinical and pathological heterogeneity that characterizes CJD in its early symptomatic stages argues against any broad generaliza-
tions based on individual case studies. Nevertheless, continuing investigation might eventually lead to a delineation of some relatively distinct neuropsychological subtypes that emerge early on, before giving way to a global dementia.

Despite the obvious logistic difficulties, the study of the rare but genetically homogeneous cohorts of familial CJD and other inherited prion disorders offer a unique opportunity to understand the relationship between initial lesions and symptomatology/objective findings. Since these latter forms of prion-induced neurodegenerative disorders may be less encumbered by imponderable epigenetic factors either modulating or dictating specific clinical manifestations, they provide an invaluable approach to the analysis of some of the mechanisms that determine the heterogeneity in the clinical manifestations of the prion disorders. This provides a strong incentive to pursue more detailed, ideally serial, neuropsychological analyses among both healthy and symptomatic members of families carrying spongiform encephalopathy-linked mutations (e.g., Unverzagt et al., 1997).

REFERENCES


