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Case Study

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Atypical features of dementia in a patient with Creutzfeldt-Jakob disease

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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G Funds Collection

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Summary

Background: This article describes a Polish patient (female, right-handed, age 68 at onset) diagnosed with the Heidenhain variant of Creutzfeldt-Jakob Disease (HvCJD), characterized clinically by isolated visual disturbances with no ocular dysfunction prior to the development of myoclonus and other symptoms of CJD.

Case Report: Nothing in the history pointed to iatrogenic or acquired CJD, and genetic testing ruled out familial CJD. The neuroradiological picture (MRI) showed non-specific features of cerebral atrophy (cortical and subcortical). An EEG revealed periodic triphasic sharp waves, particularly in the occipital lobes, and myoclonus occurring synchronically with generalized periodic epileptiform discharges. Comprehensive neuropsychological testing documented rapidly progressive dementia, with dysgraphia and aphasia deteriorating to organic mutism. Post-mortem neuropathological examination confirmed spongiform encephalopathy, especially in occipital cortex, with amyloid plaques but without neurofibrillary tangles.

Conclusions: Over the crucial 6-week period the patient went from "Mild Cognitive Impairment" to a status resembling the final stages of Alzheimer's disease, without any evidence of a CVA. The only aspect of this case that does not fit the usual criteria for the Heidenhain variant is the fact that the patient survived over a year in a persistent vegetative state. Ophthalmologists and family physicians should be aware of the possibility of HvCJD in any patient over 60 presenting with otherwise inexplicable visual disturbances in the absence of significant ocular pathology, even when other symptoms of dementia may not be immediately noticeable.

key words: **spongiform encephalopathy • dementia • akinetic mutism • cerebral atrophy**

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BACKGROUND

One of the rarest forms of sporadic CJD is the Heidenhain variant (HvCJD), in which vision disturbances are the first presenting symptoms [1]. Although the Heidenhain variant is sometimes diagnosed on the basis of early, prominent visual complaints in a patient with sCJD, in the strict sense we should speak of HvCJD only in the case of patients with isolated visual symptoms preceding the appearance of other clinical symptoms of sCJD, usually by several weeks or even months [2,3]. These patients typically present at an early stage with hemianopsia, not accompanied by pyramidal symptoms or lesions detectable by neuroimaging [4–6], followed by progressive metamorphopsia [7], visual hallucinations, and diminished visual acuity, culminating in cortical blindness without remarkable ocular pathology [7,8]. Decline in this variant is rapid (even for CJD), with decease usually occurring 5–7 months after the appearance of clinical symptoms.

The Heidenhain variant is sufficiently rare that most reports dealing with HvCJD to date have been case histories [3,5,6,8–12]. In 2005, Cooper et al. [2] performed a retrospective study of 594 neuropathologically confirmed cases of sCJD in the UK, and found 22 cases in this material that met the clinical criteria for the Heidenhain variant (3.7%).

Like all other forms of CJD, the HvCJD is a spongiform encephalopathy that requires neuropathological results for definitive diagnosis [13,14]. In post mortem studies it is characterized by changes occurring first and foremost in the occipital lobe [4,10,11]. The clinical features of HvCJD are fully consistent with the inference based on neuropathological findings, i.e. that the degenerative process in this variant begins in the occipital lobe and spreads forward [8], just as the most prominent clinical feature of early Alzheimer's disease (loss of working memory) almost certainly results from the fact that the degenerative process in AD begins in the medial temporal lobes and the hippocampus (i.e. in the "hippocampal complex"). In both AD and HvCJD, however, it remains unclear why this or that part of the brain is the point of initial attack.

CASE REPORT

The present study constitutes a return to a case of HvCJD previously described by the authors as a preliminary report, while the clinical diagnosis advanced at that time [8] has since been confirmed by post-mortem neuropathological results. There are two reasons why this case may be of particular interest:

- first to all, the authors were able to perform a considerable amount of neuropsychological testing before the patient lost logical contact, which is unusual in CJD, since neuropsychologists are seldom called in until the diagnosis is certain, by which time the disease is so far advanced that cognitive testing is impractical or impossible [15];
- secondly, the patient survived rather longer than is ordinarily the case in HvCJD, this being in fact the only reasonable objection to the clinical diagnosis of Heidenhain variant.

The patient whose case will be described here (initials JR), a right-handed Polish female, was 68 years old at the moment of onset. She had been a widow for ten years after her husband died of cancer. Her previous medical history was unremarkable (overweight, mild hypertension controlled by medication, instability of the cervical spine), and none of her parents, siblings, or grandparents were known to have had a dementive illness or to have died prematurely, though no death certificates or other medical documents were available to the authors to certify this assertion by the patient's family. None of her children or grandchildren have to date developed any neurological or psychiatric illnesses. An exhaustive investigation of the patient's history did not reveal any of the known risk factors, genetic or environmental, for acquired CJD, including previous surgery. She seldom ate meat and especially disliked beef (most Poles of her generation prefer pork). As a young woman, she worked for several years in a factory that manufactured animal hair brushes for export, so she may have had some contact with animal byproducts (including bovine) and chemical agents of various kinds; however, this had all taken place almost half a century before the onset of the disease, and at any rate there is absolutely no evidence that such a route of transmission would be possible [16,17]. It cannot be ruled out, of course, that she may have taken vitamins or medications in capsules made of beef-derived gelatin, but the same could be said for any Pole in her age group.

In the spring of 2000 there occurred a series of minor events that in retrospect may have been early indications of changes in the brain. In March of that year, after a short walk uphill, JR suddenly began to sweat very profusely, from the head only, though she was generally in remarkably good physical condition for a woman her age and did not feel especially fatigued. Since the sweating subsided within a few minutes, she told her family what had happened, but did not seek medical attention. The sweating did not recur, and the whole incident was only recalled later, when the authors were pressing the family for any information that might have indicated early problems.

The family also reports, again in retrospect, that there were noticeable changes in JR's personality during the summer of 2000, when she began to be uncharacteristically short-tempered and quarrelsome. She also appeared to lose interest in previous avocations and pastimes; though she had been known to be a very lively person, always ready for an adventure, she began to sit at home alone for days on end. It was not until mid-September, however, that increasing problems with her vision prompted her to seek medical attention, when her family physician referred her to an ophthalmologist. Her initial complaint was that when she looked through the window of her apartment, automobiles and other objects on the street seemed at various times to be either much closer than they were in reality (macropsia) or much farther away (micropsia).

By early October she had almost completely lost visual perspective, while visual images began to be seriously distorted in shape, as well as size (metamorphopsia). She first reported that many distant objects looked as though they had been flattened; later, she was alarmed when her daughter's face appeared to her very distorted, repulsive, virtually unrecognizable, with all the features out of place. The family observed during this period that she had discarded all her red towels and replaced them with dark blue; when asked why she had done this, she replied simply, "The red

Table 1. Results of standard neuropsychological tests in October, November, and December 2000.

TEST	Examination			
	Scale	Early October	Mid-November	Late December
Wechlser Adult Intelligence Scale – Revised				
Verbal	100	97	75	25
Non-verbal	100	95	61	15
Composite	100	96	68	20
Wechsler Memory Scale – Revised				
Immediate logical memory	24	21	15	3
Delayed logical memory	24	20	16	2
Immediate visual recall	41	36	28	5
Delayed visual recall	41	30	22	2
Western Aphasia Battery – Revised				
Aphasia Quotient	100	98	75	22
Cortical Quotient	100	86	55	12
BNT				
Anomia score	60	49	41	9
Cracow Right Hemisphere Diagnostic Battery				
Agnosia	100	94	73	12
Constructive apraxia	100	87	41	3
Dyspragmatism	100	95	59	10
Perseveration	50	45	31	14
MMSE				
Global score	30	21	9	2

ones hurt my eyes." In mid-October she complained that she sometimes saw black spots before her eyes, especially when she looked at a white wall; by late October she was describing these black spots to the family as resembling insects climbing the walls. She was fully aware that the black spots were not in fact insects, but rather used the metaphor of "black bugs" to describe their appearance, often in a joking manner.

Memory lapses were becoming more common and more troublesome, especially when on one occasion she could not remember her daughter's name. At this stage of the disease, the patient was referred for neuropsychological consultation to the first author of the present study, and systematic neuropsychological testing was immediately commenced (a summary of results is given in Table 1). When tested in October using the Western Aphasia Battery-Revised [18], JR's aphasia quotient was in the normal range, but the cortical quotient (a measure of cognitive performance related to language), at 86, was slightly below normal for her age and education. Her speech in conversation was characterized by frequent transpositions and contaminations, which if more pronounced would have been consistent with a diagnosis of either conduction aphasia or apraxia of speech (in subsequent examination these problems increased in severity, and the word-finding problems were less and less often self-corrected, cf. Table 1). It was also noticed that she showed hesitation in some naming tasks, and scored only 49/60 on the Boston Naming Test [19], where a healthy normal individual should have at least 55/60. Occasional word-finding problems were also noticed in ordinary conversation. She was generally aware that these problems were occurring and was eager to cooperate in finding solutions. She was able to read single words and short sentences without difficulty or hesitation, but when the sentence was longer than one line on the page she had difficulty finding the start of the next line, and not infrequently complained that the sentence was "just a pile of words, with no sense."

Her composite IQ measured by the Wechsler Adult Intelligence Scale-Revised [20] (WAIS-R-pl [21])was comfortably within the normal range (96). She had considerable difficulty in performing simple arithmetic, however, and was unable to complete all but the very simplest block pattern tests; otherwise, her IQ would have been slightly above 100. On the Wechsler Memory Scale-Revised (WMS-R [22]), her results for delayed verbal memory and visual recall were over 2 standard deviations below Polish norms for

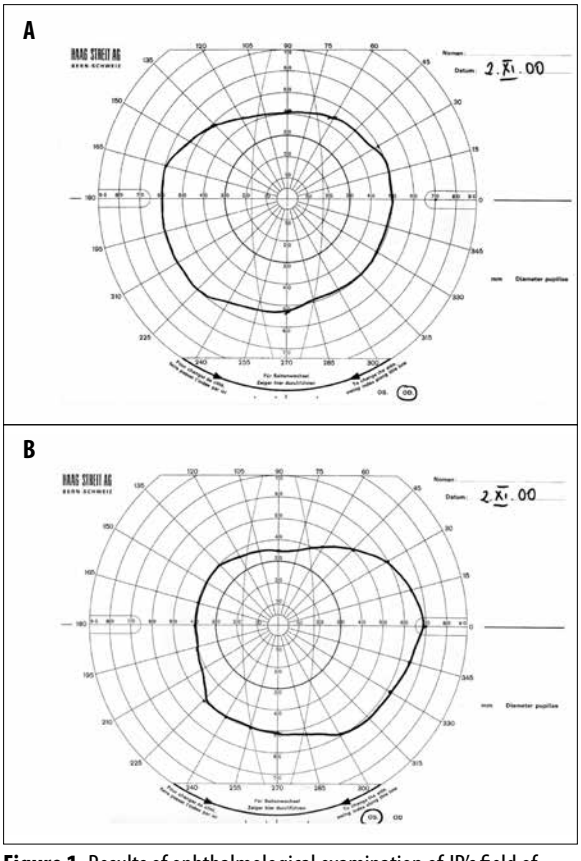


Figure 1. Results of ophthalmological examination of JR's field of vision, 2 November 2000, indicating hemianopsia. (**A**) right eye; (**B**) left eye.

her age group [23], indicating abnormally rapid deterioration of the memory trace over a 20-minute filled interval. On the Cracow Right Hemisphere Diagnostic Battery [24] she had slightly below-normal scores on the subtests measuring agnosia, constructive apraxia, dyspragmatism (an inability to adjust the content of an utterance to the context in which it is spoken [25]), and perseveration, but even so her results at this stage were well above the range typical for patients with right hemisphere strokes.

On the Mini-Mental State Examination (MMSE [26]), a widely used screening instrument for dementia, JR in mid-October achieved a score of 21, placing her in the range above the usual upper limit for dementia, but well within the range of "mild cognitive impairment." Points were lost primarily in orientation in time, remembering three words after a filled interval, and the drawing task. When asked to take a piece of paper in her left hand, fold it in half, and place it on the floor (a task from the MMSE), she took the paper in her right hand and folded it, but did not place it on the floor, strenuously denying that she had been instructed to do so.

Her handwritten monthly budgets and notes to herself written in October and November of 2000, recovered from her apartment by her family and made available to the present authors, point to increasing neuropsychological problems [8]. In November, shortly before her hospitalization, JR's attempt to pay her monthly bills at the post office ended in a quarrel with the clerk, after which she finally relented and allowed her son and daughter to begin handling her financial affairs.

In mid-October a test of JR's visual field performed by the third author of the present study showed slight left hemianopsia without hemiparesis or other neurological symptoms of cortical brain damage [12] (cf. Figure 1). Her gait had slowed considerably, but this seems to have been the result of anxiety associated with navigating through a strange and unstable visual environment. Later on, she began to show increasing unwillingness to leave home, even to do her daily shopping; she explained to her grandson that when she walked, she saw the earth opening before her feet, and was afraid to take another step. By this point, JR had begun to have other hallucinations as well, including a gradual shift from using "black bugs" as a metaphor to describe the black spots before her eyes, to active hallucinations of cockroaches climbing over her body and her food [8].

In mid-November, in view of increasing gait problems and her inability to care for herself at home, she was hospitalized in the Department of Neurology at the Ministerial Hospital of the Polish Ministry of Internal Affairs and Administration in Cracow, under the care of the second author of the present study. A CT scan performed at this time by the fourth author revealed discrete dilatation of the posterior horns of the lateral ventricles, slightly more on the right than on the left (in later scans, the asymmetry shifted leftward). Apart from these anomalies, there were no other pathological findings at this point. Standard laboratory tests (including culture and microscopic examination of the CSF) likewise produced no remarkable results.

The family, nursing staff and fellow patients reported that JR was showing an increasing tendency to monologize. By the end of November her MMSE score had dropped from "mild cognitive impairment" (21 points) to "severe dementia" (9 points), a remarkable decline over one month; on other neuropsychological tests, however, the changes, though marked, were not as drastic in comparison to the October results. Her composite IQ was now 68, lower in the non-verbal component than in the verbal, but rather higher than a finding of "severe dementia" on the MMSE score would lead one to expect. There was further deterioration on the WMS-R, without significant change in the proportion of the various components (verbal and non-verbal, immediate and delayed, with non-verbal slightly worse than verbal, and delayed much worse than immediate). On the WAB-R, however, JR's score was now in the aphasic range, with the cortical quotient again noticeably lower than the aphasia quotient. Although the results of the subtests were too mixed to give a clear picture in terms of the WAB's diagnostic criteria, there was a general tendency to impaired comprehension and verbal paraphasias, suggesting a more posterior aphasia. Her problems with naming increased on the BNT (41/60), and it was observed during administration of this test that priming – i.e. prompting with the first syllable of the target word, or with semantic clues – did not help her to recover the lost name (ineffective priming is often listed as a characteristic feature of Alzheimer's dementia [27]).

JR's scores on the Cracow Right Hemisphere Diagnostic Battery also went down considerably in comparison to mid-

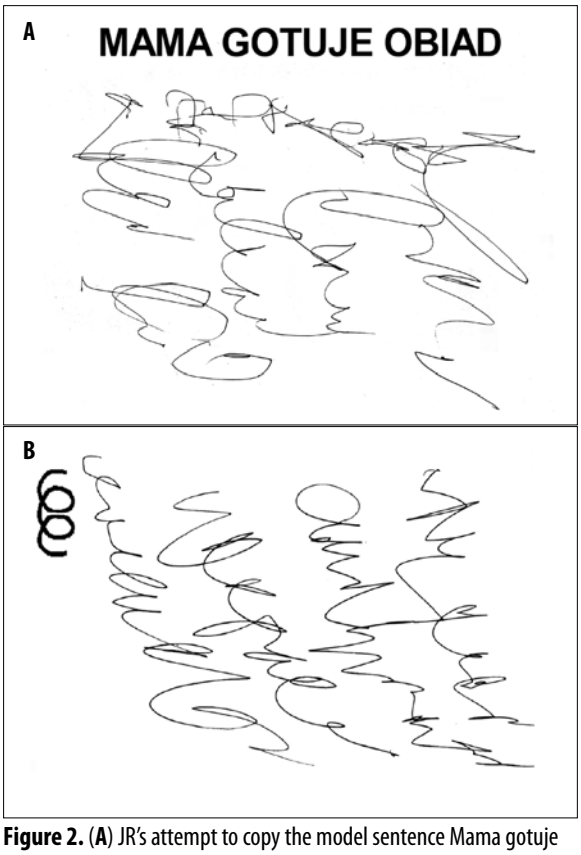


Figure 2. (**A**) JR's attempt to copy the model sentence Mama gotuje obiad 'Mama is cooking dinner', December 12, 2000. (**B**) Perseveration test, JR, December 12, 2000. The task was to make five exact copies of the model figure drawn in the upper left corner. Perseveration may appear as more than three loops in each figure (as here), more than five figures, or both.

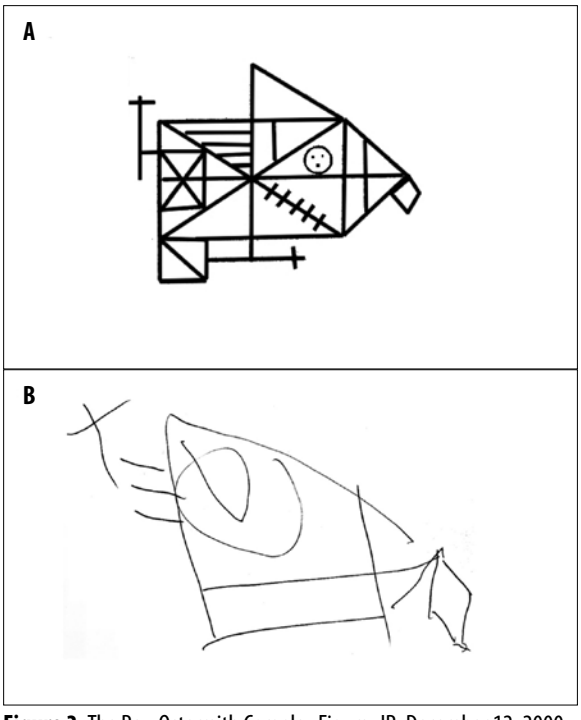


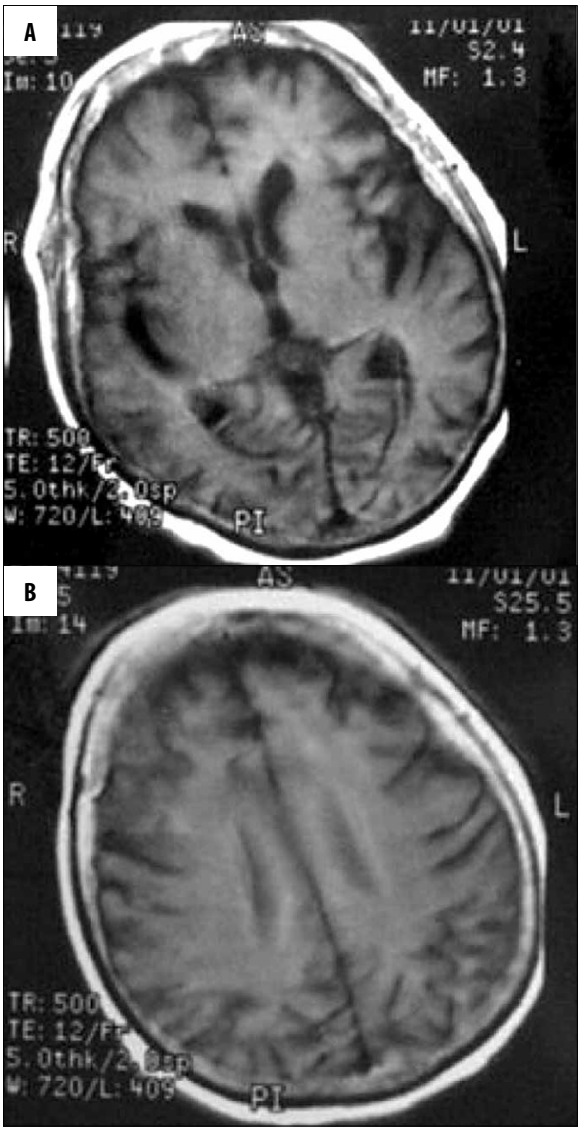
Figure 3. The Rey-Osterreith Complex Figure, JR, December 12, 2000. The task was to copy the model (**A**); the patient drew figure (**B**) in response. When asked to draw the figure again from memory 15 minutes later, JR stated that she could remember nothing.

October (cf. Table 1). In particular, she was observed to have serious difficulties with pragmatics: inability to maintain the topic of conversation, violations of turn-taking rules, abrupt and unmotivated termination of conversations, etc.

On December 1, 2000, a follow-up MRI examination was performed under the supervision of the fourth author of the present study. The examination was performed in SE T1, PD, FSE T2, and FLAIR sequences, and SE T1 after intravenous administration of a contrast agent (Magnevist), in the sagittal, coronal, and horizontal planes, in 3- and 5-mm slices. In the corona radiata bilaterally there were isolated, small foci, probably representing areas of demyelinization. Large Virchov perivascular spaces were visible in the central right and posterior left putamen. Considerable atrophy could be seen, with a predominance of subcortical changes in the left hemisphere, and cortico-subcortical changes in the right hemisphere. The cortical atrophy was especially pronounced in the frontal and occipital lobes.

When interviewed again by the present authors in the second week of December, just before she was sent home from the hospital on furlough for the Christmas holidays, JR did not maintain eye contact with the examiner and frequently rambled off the subject. Her sentences often trailed off unfinished, and when prompted to continue she complained that she could not remember what she had meant to say. When asked to copy the sentence *Mama gotuje obiad* 'Mom is cooking dinner,' she produced only a series of scrawls filling the entire page (see Figure 2A). Figure 2B shows her response to the command, "Please make 5 exact copies of this figure" (the prompt is shown in the upper left corner); JR perseverated the loops, made only 4 figures, and obviously has only minimal control over the pen. When asked to copy the Rey-Osterreith Complex Figure (Figure 3), she made a very desultory effort; after a 15-minute delay she stated that she could remember nothing of the figure and refused to even try to draw it from memory.

Within a week after this interview, she fell into a state of hallucinosis, now without any criticism. When actively hallucinating she was highly agitated, fearful, disoriented, and almost completely unresponsive to questions or commands. In view of the rapidity of the mental deterioration, the decision was made to test the patient for possible CJD, and a sample of her CSF was sent to the Creutzfeld-Jakob Disease Laboratory at the University of Göttingen to test for the presence of the 14-3-3 marker protein [28], a common finding in CJD patients and confirmed in all but one [6] of the HvCJD cases reported in the literature [29]. Genetic testing performed during this same period of time at the Institute of Neurogenerative Diseases at the University of California, San Francisco, under the supervision of Prof. Stanley Prusiner, found that the most common polymorphism responsible for the genetically transmitted variants of CJD (at codon 129) was not present. Bacterial and viral encephalitis were ruled out, as well as neoplastic disease, fronto-temporal dementia,



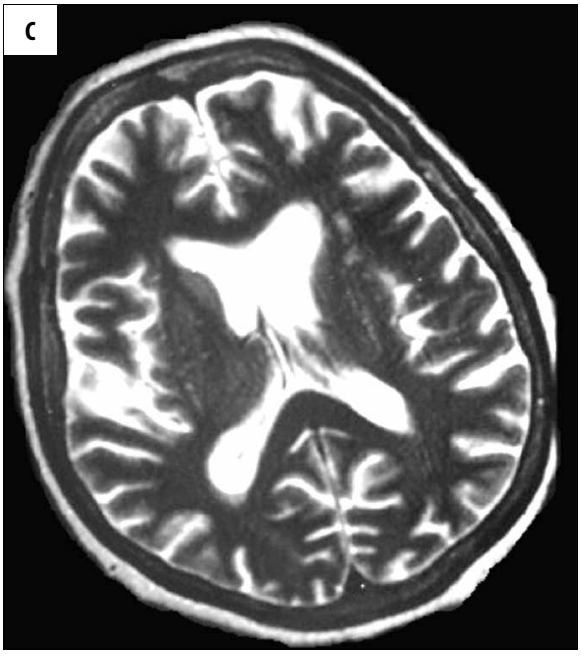


Figure 4. Magnetic resonances images of JR's brain, 11 January 2006, approximately 4 months after onset of first visual symptoms. Generalized cortical atrophy, more prominent in the occipital lobes than in previous examinations.

and Pick's disease. The rapid and dramatic course of the disease, the fact that the first presenting symptoms were visual disorders, and the exclusion of other possibilities more and more strongly pointed to HvCJD. The results of the test for 14-3-3 were returned positive in January 2001, which led to a clinical diagnosis of CJD (ultimately confirmed by post-mortem neuropathological findings).

The tempo of mental and physical deterioration began to accelerate markedly after the Christmas holidays. Standard neuropsychological tests were administered for the last time in late December 2000 (see Table 1). By this time JR had only 2 points on the MMSE (she remembered one of the three words she was asked to repeat, and on the triple command task she picked up the piece of paper). The WAIS-R was very difficult to administer, as was the WMS-R, and the scores were minimal. The WAB showed a profound posterior (sensory) aphasia. On the BNT, she was able to name only 9 of 60 pictures, and that with considerable hesitation.

By early January the patient was bedridden with severe left hemiparesis; she reacted only to large, red objects as visual stimuli, so the first author adapted a number of exercises in order to work with her. She recognized and correctly identified some of the large red cut-out figures, though her verbal output was now scanty and barely audible. When asked to point to geometrical figures specified by the examiner (again, large and red) she was sometimes able to comply; in order to look at the test cards, she turned her head sharply to the right and rotated her eyes sharply to the left, and her responses were slow, hesitating, and faltering. In conversation she answered direct questions with a significant delay (1–5 seconds), using only one or two words at most in response to simple direct questions; when a more elaborate answer was needed her only reply was to shake her head or wave her hand. She could repeat no more than three or four words. Attempts to stimulate further speech production met with resistance: JR clamped her teeth in response and refused to open her mouth, even to eat. This behavior was interpreted by the family to mean that she did not wish to speak with them and was punishing them for returning her to the hospital after the Christmas furlough. Her verbal output dwindled and finally disappeared. For a brief period in mid-January she remained minimally and sporadically responsive to simple verbal commands, but within a week logical contact was completely lost.

A repeat MRI examination was performed on January 11, but JR was very restless in the tunnel and could not be induced to lie still. Enough images were readable, however, to indicate that that the deterioration of neural tissue in the occipital lobes had advanced considerably (Figure 4) [14]. An EEG performed by the second author several days later showed the periodic triphasic sharp waves characteristic of HvCJD [10,12,30], particularly in the occipital lobes, and myoclonus occurring synchronically with generalized periodic epileptiform discharges, consistent with the clinical diagnosis of HvCJD.

By this point the myoclonus and hyperkinesia typical of advanced CJD]2,10,12] had become very pronounced and nearly constant. She reacted to sudden sharp noises after a long delay, slowly raising her right arm until it was perpendicular to the trunk, and then holding it there until it was moved by some outside force (catatonia). She still had obvious sleep-wake cycles, and her eyes were often open during the day, but she did not follow movements, react to light, or look in the direction of a sound stimulus. An ophthalmological examination performed by the third author showed cortical blindness: there was no reaction to any visual stimulus, but the eyeball itself and the optical nerves up to the optical chiasmus seemed to be intact. The pupillary reflex was not extinct, but it was very sluggish. When her eyes were open, both eyeballs moved symmetrically in a repetitive jerking rhythm upward and to the left.

In view of the typically rapid progress of the disease, there was a general expectation at the end of January 2001 that death would follow very soon. However, the hyperkinesia and myoclonus largely receded, and JR's clinical status went from akinetic mutism to a persistent vegetative state, when the swallowing reflex disappeared and parenteral feeding was necessary. This state continued for nearly a year and a half, until her death in June 2002. Several potentially dangerous infections developed, but were successfully managed. Throughout this period she remained hospitalized under the care of the second author. JR's family visited daily, especially her daughter and her son, who took an active supporting role in providing palliative care.

The post-mortem examination confirmed the clinical diagnosis of HvCJD on the basis of neuropathological results: spongiform degeneration without neurofibrillary tangles, especially in the occipital lobes (Figure 5).

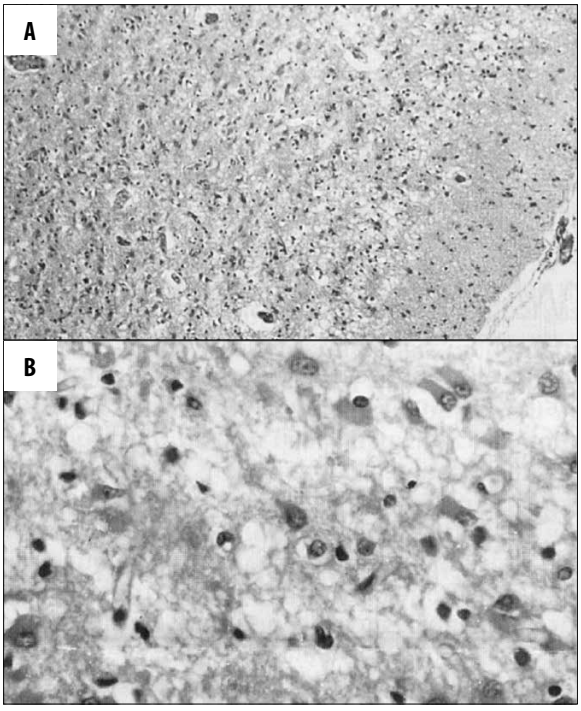


Figure 5. Neuropathological results from the post-mortem examination of JR's brain, showing spongiform encephalopathy. (**A**) HE stain, magnification 200×, gray matter from the occipital lobes; (**B**) HE stain, magnification 1600×, neutrophils.

Discussion

The case described here shows all the clinical features of the Heidenhain variant of Creutzfeldt-Jakob disease, with the exception of the relatively long course. The patients described by Tsuji et al. [5] and Fauquembergue et al. [3] lived for more than a year after the first symptoms were noted, but most other HvCJD patients described in the literature have lived for only a few months or even weeks after onset; in the case reported by Rizzo et al. [9], the patient died within 4 hours after admission. The only other anomaly of note is that our patient, in contrast to all 22 of the HvCJD patients described by Cooper et al. [2], was not homozygous for methionine at codon 129. The MRI examination in December did not show the preponderance of atrophy in the occipital lobes that one might expect, but both the January MRI (see Figure 4) and macroscopic examination during the post-mortem showed the usual pattern. As pointed out by Thomas et al. [14], there is reason to suppose that the changes in the brain brought about by the progress of CJD are initially neurodynamic, with structural changes occurring later, which is borne out in the present case.

There are several other aspects of this case that would seem to merit further discussion. For the present purposes, however, we would like to call particular attention to:

- the gradual transition from black spots in the field of vision to hallucinated insects, apparently mediated by a metaphor;
- rapid progression from a posterior aphasia to organic mutism.

The progression from visual disturbances to hallucinosis

The evolution of hallucinosis in this case is of particular theoretical interest [8] from a neuropsychological perspective. The steps that led from a visual disorder (black spots on a white background) to hallucinosis are clearly mediated by language. JR's way of speaking about the visual phenomenon made a steady progression:

- "black spots on the wall." Initially JR was simply reporting a visual phenomenon, which troubled her precisely because she knew, contrary to what her eyes seemed to be telling her, that in reality there were no black spots on the wall. When a healthy adult sees a pencil in a glass of water, the image appears broken, but no matter how convincing the appearance, it does not overcome the cognitive awareness that the pencil is not broken [31];
- "black spots that *look like* bugs." JR used a simile, more or less humorous in intent, in an effort to explain to others what she was seeing, since, as she correctly assumed, they did not see the same thing. Theoretically speaking, similes place an overt disjunction between subject and predicate: the statement, "X looks like a real bug" rather clearly implies that X is not a bug, but if we say to someone, "You look like a fool," it is unlikely that a similar inference will be made;
- "black bugs on the wall." Here the simile has been compressed into a metaphor [32]: the word "like" is omitted,

and the expression "black spots" is replaced by "black bugs." Gradually the visual phenomenon is re-named, and the planes of literal and transferative meaning begin to be confused;
- "black bugs climbing up the wall." When the metaphor is understood literally, the designate *becomes* that which it is called. This is no longer a visual disturbance, probably resulting from fatigue of the rods and cones in the retina, but a visual hallucination: JR *saw* black bugs, which were not there. Moreover, there was a crossing of modalities, as she began to feel the bugs crawling over her skin (other authors have remarked an unusual combination of visual and tactile hallucinations in CJD patients [33]).

The pathological visual image is thus transformed into an hallucination when its name becomes a literal designation rather than a metaphor [34], at which point it would be proper to speak of "organic hallucinosis" according to ICD=10 criteria [35].

Rapidly developing organic mutism

The very rapid cognitive and neurological decline that occurred in JR's case over a six-week period is perhaps the most obvious clinical feature of CJD, the one most likely to arouse suspicion that a demented patient has one of the various CJD variants. This course differs fundamentally from sudden onset, as in the case of a stroke or traumatic brain injury, where ischemia, edema, or tissue destruction by a foreign object leads to necrosis in a matter of minutes or at most hours; it also differs from the slow but steady decline typical of other degenerative diseases causing dementia, such as Alzheimer's Disease, where the development of symptoms may be a gradual process lasting several years or even more than a decade. Indeed, the declining results shown in Table 1 would be typical for dementia of the Alzheimer type (DAT), if the successive tests were given at intervals of one year, and not one month.

In the case described here, this unusual acceleration of symptoms is very evident in the way dysgraphia became a posterior aphasia, which quickly developed into organic mutism, defined here according to Lebrun [36] as the absence of oral-verbal expression, along with neurological deficits suggesting CNS damage, in the absence of evident psychological problems. The patient's speech production deteriorated from near-normal (with occasional word-finding problems) to organic mutism within a matter of 3–4 weeks. The successive stages included word-finding difficulties, developing through paraphasias, agrammatism, and telegraphic speech, to organic mutism. This was an extremely rapid process, but then again, not an abrupt change, as occurs in post-stroke or post-traumatic aphasia. In other words, there was not a single event that destroyed a brain region essential for speech production, nor was there a gradual decay, as in more typical cases of dementia. On the other hand, the loss of speech was clearly of organic origin: the family's interpretation of her silence as intentional can safely be rejected in view of the entire clinical picture. The process can perhaps best be described as an accelerating collapse. This would seem to be consistent with the geometric acceleration characteristic of spongiform encephalopathy generally, and the prion diseases particularly.

Towards a microgenetic theory of dementia

Modern neuropsychology is largely based on an essentially modular, more or less explicitly cognitivist approach to brain work: that is, the brain is assumed to be a kind of organic computer, consisting of a hierarchical system of processors, each of which performs a discrete function and is connected to other processors by transmission lines. Thus particular mental states are understood as outputs, the sum or product of a finite series of functions (understood here in the mathematical sense, where the same input always produces the same output), performed by neural centers ("processors") that in a specified sequence receive input data from a given source, perform their functions, and then pass on the output data to the next processor, or (ultimately) to the executive apparatus, i.e. the peripheral nerves that effectuate behavior.

The current dominance of this general model of the brain is a product not only of the "computer revolution," which has made such concepts as "input," "output," and "processor" familiar to most educated people, but also of the history of neuropsychology, which in an important sense began with aphasia studies in the 19th century and the resultant identification of the speech centers in the brain, still known as Broca's area and Wernicke's area. Like the geocentric universe before Copernicus and Galileo, the modular brain [37] seems to be so completely consistent with common sense and so universally accepted that only a heretic would question it. Mapping the brain (even if the results are sometimes unsettlingly similar to the phrenological charts of the early 19th century) seems as legitimate a project as mapping the genome.

Modular brain theories are largely based on evidence from lesion studies, which received a major impetus in the late 1970s from the appearance of computer tomography and magnetic resonance imaging. It was now possible to correlate structural changes in the brain of a living patient (previously hypotheses could only be verified by autopsy) with neurobehavioral symptoms, in an effort to confirm the presumed links between disturbed mental processes and specific brain functions performed by processors located in anatomically identifiable brain regions. This in turn has caused the majority of attention in neuropsychology to be focused on studies where hypotheses concerning the location of processors could be advanced and tested: that is, on patients with isolated, detectable lesions. Dementia, with its complex pathomechanisms and typically non-specific neuroimaging picture, has thus played a relatively minor role in the formation of neuropsychological theory. This may be at least in part due to the fact that a consideration of the course of dementia, as in the case of JR described here, raises some serious and unsettling questions about the validity of the modular paradigm, which may have outlived its usefulness [38].

Microgenetic theory, which is based on process thinking and the philosophy of Sir Alfred North Whitehead, has been introduced to neuropsychological theory by Jason W. Brown [39,40]. At present it constitutes perhaps the only viable alternative to the modular approaches inherited from Wernicke and Lichtheim. The basic assumption of the theory is that a given mental state results from a process called "microgene-

sis," which unfolds over a fraction of second through layers of processing that represent phases of transition in the development of the central nervous system, following the paths laid down by phylogenesis and ontogenesis. What is essential in understanding mental process is the flow of time and the generally stable series of transformations that sculpt primitive reactions and reflexes into complex mental processes. Lesions and neurodegenerative diseases cause different symptoms, not because of the particular processors that are damaged or destroyed, but because of deflection or delay in particular segments of the unfolding mental process. Thus dementia is best understood as a devolution, a kind of entropy that slows, distorts, and ultimately disorganizes mental process.

In the present study, of course, we can hardly enter into a comprehensive discussion of the weaknesses of modular approaches, or the complexities of microgenetic theory. It may be useful, however, to take another look at the progression that took place in JR's case, from specific distortions of the visual image to visual hallucinations, with clinical symptoms generally preceding the appearance of changes detectable by MRI.

In order to understand the decay of visual perception that occurred in JR's brain as the disease progressed, a few essential definitions are required. By *perception* we mean not so much the reception in the brain of relatively reliable and relatively complete sensory data pertaining to an object, but rather the process by which an image or representation becomes a comprehensible object, something that can be grasped by the conscious mind. There are, of course, many kinds of mental objects, including memories, fantasies, and abstractions. Perceptual objects are those which arise in the mind in response to sensory data (that is, transduced signals sent to the brain after some kind of physical stimulus has aroused a receptor somewhere in the peripheral nervous system). It is important not to confuse the perceptual object with the thing itself, though our daily functioning in the real world usually depends on our implicit faith that the things we see (hear, feel, taste, smell) are real and exist in the world outside of our minds. In dream and hallucination, of course, there are perceptual objects that appear in consciousness independent of immediate sensory data, but they are still objects. The relationship between perceptual objects and abstractions or categories is philosophically very complex [31,41], but for the present purposes we can safely bypass the issue, at least for now.

Perception, then, as here defined, is dependent on consciousness. A patient under general anesthetic feels no pain, not because there is no painful stimulus, but because consciousness is suppressed and there is no awareness of what is happening. In the absence of consciousness there is sensory data, but no object, which would be pain if the individual were conscious. Analogously, a person can look directly at a thing and yet not see it (for example, in the case of a well-camouflaged animal in the forest), which means that the object exists in the world, but not in the mind, and thus there is seeing (the eyes are working, as is the optic nerve), but no perception, because the brain does not make the sensory data into an object.

Consistent with the basic assumptions of microgenetic theory, as briefly sketched above, the object that finally appears in consciousness as the result of perception has been formed over a series of transformations taking place in microgenesis [34]. In deep, dreamless sleep, there are no perceptual objects at all, but the peripheral nervous system is in a state of readiness and can be aroused (which distinguishes deep sleep from anesthesia or coma). When the nervous system is somewhat more active, objects appear spontaneously in the mind without immediate sensory stimulation, based largely but not exclusively or strictly on memory, and we dream. The fact that dreams are invariably accompanied by affect points clearly to their limbic origin, i.e. to a level in phylo-onto-microgenesis that is deeper, and thus older, than the neocortex. When the brain brings into the sphere of consciousness objects derived from past perception, we speak of memory; when the objects are in some way inferred, of imagination [41]. In either case, the healthy adult brain is capable of discriminating perceptual objects from that which is remembered or imagined; when this distinction is blurred, one experiences flashbacks (as in post-traumatic stress disorder) or hallucinations. The latter are especially destructive to consciousness, which is why their appearance in schizophrenia or advanced dementia almost invariably signals psychosis, requiring immediate intervention.

The foregoing implies that the perceptual object is not assembled in the neocortex directly from the raw data supplied by the sensory receptors, but rather emerges in a series of stages, where sensory data and memory serve to sculpt a primitive *Gestalt* into a specific object. On the lower levels of the central nervous system, objects are not yet fully sculpted into detailed objects, but rather assigned to rough, broad categories, which become increasingly more complex and detailed as microgenesis proceeds upward. Primitive percepts are closely, indeed inextricably tied to behaviors, while at higher levels the stimulus-response bond becomes more tenuous, as perception and action become more independent [34,42,43]. Most of what occurs in microgenesis is thus under the surface, invisible, "subconscious" or "unconscious." Our implicit faith in the veridical nature of our perception comes from the acceptance "on faith" of the surface manifestation, regardless of whether or not we understand its antecedents.

Having the foregoing theoretical reflections in mind as a kind of backdrop, it is possible to explain the progress of JR's visual disturbances in microgenetic terms, as the perception process "unravels" from surface to depth. Initially, then, macropsia and micropsia, the first presenting symptoms in this case, are disorders occurring at the surface, just at the point when the object has taken shape but is not yet situated in mental space. Metamorphopsia, which followed, represents a slightly earlier stage in the microgenesis of the perceptual object, causing the object to be not only misplaced in three-dimensional space, but also distorted in two-dimensional planes. The black spots, then, which JR originally understood to be "non-objects" resulting from a visual disorder, became hallucinations precisely when she lost the awareness of their origin, and they become "black bugs"; significantly, as microgenetic theory would predict, this transition is accompanied by anxiety and finally panic when all criticism is lost, indicating the increasing involvement of the limbic system in the degeneration process. Finally, the last step in this process before the permanent loss of consciousness was cortical blindness, when the pri-

mary visual cortex in the occipital lobes could no longer accept any data at all from the eyes and the optic nerve. A patient with cortical blindness "sees" objects which the brain produces of its own accord, and is typically unaware that these percepts are not veridical.

This sequence of events is paralleled, with a certain delay, by the neuroimaging results. In the December MRI, there were non-specific changes that would not suffice to explain the visual symptoms that were already fairly well advanced, while the January MRI shows significant deterioration of the occipital lobes, consistent with cortical blindness. This suggests that the disease process is initiated by dynamic, functional changes, with structural changes visible in MRI following later, as disuse leads to apoptosis and neuron loss, accumulating to spongiform encephalopathy.

CONCLUSIONS

In the case reported here, a clinical diagnosis of the Heidenhain variant of Creuzfeldt-Jakob Disease, initially suggested by the early and prominent presentation of visual symptoms (ranging from microopsia and macropsia to visual hallucinations), and backed by EEG and neuroadiological findings, was confirmed by neuropathological results. Neuropsychological testing documented the characteristically rapid course of the disease. The course of development of clinical symptoms and their relationship to the ophthalmological and neuroradiological picture are of considerable theoretical interest.

Ophthalmologists and family physicians should be aware of the possibility of HvCJD in any patient over 60 presenting with otherwise inexplicable visual disturbances in the absence of significant ocular pathology, even when other symptoms of dementia may not be immediately noticeable.

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