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Acquired Organic Mutism in the Course of Creutzfeldt-Jakob Disease (Heidenhain Variant): A Case Study

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This article describes the onset of mutism in a patient with the Heidenhain variant of Creutzfeldt-Jakob Disease (Hv-CJD), where vision disturbances are the first presenting symptoms. In this case, the development from the onset of the first detectable speech and language symptoms to acquired organic mutism was progressive but very rapid. The first presenting symptom was dysgraphia (shown in documents from summer 2000), then varied and progressive visual disorders culminating in hallucinations. Very rapid neurological and neuropsychological deterioration (dementia) occurred in December-January, leading to organic mutism. The neurolinguistic significance of the findings is discussed.

1. Spongiform encephalopathy: the basic pathomechanism of CJD

Spongiform encephalopathy (SE) – so called from the "sponge-like" appearance of the gray matter of the brain when viewed under light microscopy (Mastrianni & Roos, 2000) – is a common neuropathological finding in many degenerative diseases of the central nervous system. The clinical symptoms associated with SE, caused by the cascading effects of neuron loss, affect initially and primarily complex cerebral functions that require the cooperation of numerous centers and pathways in the brain. Thus the leading symptom of SE is most often dementia, sometimes preceded, followed, or accompanied by a variety of other neurological and neurobehavioral disturbances, including psychosis. Among the diseases that are characterized by SE are Alzheimer's Disease, several mitochondrial cytopathies, and especially the recently discovered prion diseases, which have attracted so much attention in the popular press in recent years due to the outbreak of bovine spongiform encephalopathy (BSE) in Europe and the possibility of its transmission to humans.

A prion is a transmissible pathogen in the form of a protein, which, unlike a bacterium or a virus, has no replicative elements. The name was coined by Stanley

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Prusiner, whose discovery of prions yielded him the Nobel Prize for Medicine in 1997. In the present state of our knowledge, the pathomechanism by which prions lead to SE can only be partially outlined. Prions originate from the protein known as PrP, genetically coded by the PRNP gene in the human chromosome. Normal PrP molecules (designated PrPC) are distributed primarily in the central nervous system, but their exact function remains unknown (Mastrianni & Roos, 2000; Büeler et al., 1992). When pathogenic prions (designated PrPSc) are introduced into the nervous system, they adhere to healthy PrPC molecules and transform them into pathogenic PrPSc, which, in a way that remains to be elucidated, leads to neuron death and SE. The varying mechanisms by which prions can enter the central nervous system and the varying results of their activity account for the existence of a phenotypically diverse family of prion diseases. The best known of the prion diseases is of course Creutzfeldt-Jakob Disease (CJD), characterized by rapidly progressive severe dementia, ataxia, myoclonus, hyperkinesia, and death within several months to a year after onset (Creutzfeldt, 1920; Jakob, 1921). CJD typically has a very long incubation period (8-15 years), but after the appearance of the first clinical symptoms the patient enters into a characteristically rapid decline with fatal outcome.

Several variants of CJD have been identified, of which the best known is the so-called "new variant" (nvCJD), probably a transmissible human form of BSE, the famous "mad cow" disease. By far the rarest form of CJD, however, is the Heidenhain variant (HvCJD), in which vision disturbances are the first presenting symptoms (Heidenhain, 1929). These patients typically present at an early stage with hemianopsia, not accompanied by pyramidal symptoms or lesions detectable by neuroimaging (Brazis et al., 2000), followed by progressive metamorphopsia (Kropp et al., 1999), visual hallucinations, and diminished visual acuity, culminating in cortical blindness without remarkable ocular pathology. Decline in this variant is rapid and decease usually occurs within 5-7 months of onset.

2. Case description

The patient described here is a 68-year-old right-handed Polish female. She is presently widowed, and has healthy children and grandchildren. There is no family history of neurological illnesses, and her previous medical history is unremarkable (overweight, mild hypertension controlled by medication, instability of the cervical spine). She seldom ate meat and especially disliked beef. As a young woman, she worked for several years in a factory that manufactured animal hair brushes for export, so she may have had contact with animal byproducts (including bovine) and chemical agents of various kinds. Apart from this, however, an exhaustive investigation of the patient's history has not revealed any of the known risk factors, genetic or environmental, for CJD.

Disquieting events that in retrospect may have been a kind of prodrome to the onset of HvCJD (Mastrianni & Roos, 2000) began in early 2000. In March, after a

short walk uphill, she suddenly began to sweat profusely, from the head only, though she was not especially fatigued. The sweating subsided within a few minutes and she did not seek medical attention. The family reports in retrospect that some negative changes took place in the patient'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. Significantly, an examination of her monthly rent book shows clear signs of significant agraphia emerging as early as July, which she attempted to hide from the family (cf. Pachalska et al., 2001a). Medical attention was not sought until mid-September, however, when she reported to an ophthalmologist complaining of odd vision disorders. Her initial complaint was that objects in the immediate vicinity seemed at times to be much closer (macropsia), or sometimes much farther away (micropsia), than they were in reality. By early October she had largely lost the sense of visual perspective, while visual images began to be seriously distorted in shape, as well as size. She first reported that automobiles on the street looked oddly flattened; later, she commented with consternation that her daughter's face was horribly distorted, virtually repulsive, with all the features out of place. She also displayed hypersensitivity to bright colors, especially red, which she avoided (during this period she discarded all her red towels and replaced them with dark blue). In early November a test of her visual field showed slight left hemianopsia, unaccompanied at this time by hemiparesis. Her gait had slowed considerably, but she attributed this to her difficulties in maintaining visual perspective and anxiety that she would stumble over something. Later, she complained of a feeling that a great precipice was opening before her feet, so that if she took one more step forward she would fall into a chasm.

The lists of monthly payments she prepared in October and November of 2000 (accidentally preserved and made available to the authors by the family, see Fig. 1) indicate that her neuropsychological problems were becoming more intense.

It had been her usual practice to make a list of monthly bills with the relevant amounts, which she paid as soon as she collected her monthly pension. In the October list, numerous problems can be seen. The initial letter M (Polish *mieszkanie* = *apartment*) is written twice, with the first downstroke in the second M repeated

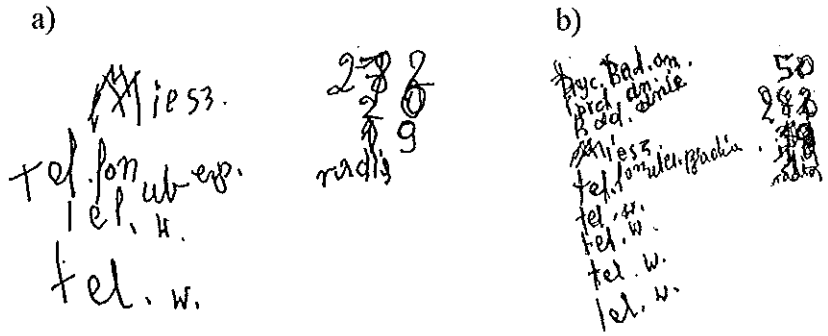

Fig. 1. The patient's monthly budget from October (a) and November (b) 2000.

several times. The abbreviation *Miesz.* is not standard. The word *telefon* is not properly aligned in column, and the period between the syllables is hard to explain. The next item, *ubezpieczenie* (insurance), is placed almost on the same line as *telefon* and broken into two elements, which are not aligned with each other. The word *radia* (presumably *radio*, normally identically spelled in Polish and English) is completely in the wrong column. The element *tel.* is then repeated twice (once with the t uncrossed), followed by a period and an inexplicable *w*, which may be of phonetic origin (w in Polish is pronounced like v, or like f in word-final position). The numbers in the second column have been written over several times and no total has been calculated. The November budget shows further deterioration: it begins with a nearly inexplicable entry that probably means "test at the clinic", with the word *badanie* (test, examination), like *telefon*, broken into two syllables by a period. This time *radia* occurs in both columns, and the figures are even more intensely written over. The perseveration of the inexplicable *tel.w.* is particularly remarkable.

At this stage of the disease, the patient was referred to our clinic, and systematic neuropsychological testing was commenced. The patient did not have aphasia at this point, and her intelligence was near normal. It was noticed, however, that she showed hesitation in some naming tasks, and in ordinary conversation she was occasionally unable to find words. Her speech was characterized by frequent transpositions and contaminations, followed later by verbal paraphasias, yet later by neologisms. In each successive examination these problems increased in severity, and the word-finding problems were less and less often self-corrected. She had difficulties with simple arithmetical operations and was unable to complete all but the very simplest block pattern tests in the WAIS-R. Delayed verbal and visual recall were over 2 standard deviations below Polish norms for her age group on the WMS-R. On the Cracow Right Hemisphere Diagnostic Battery (Pachalska & MacQueen, 2000) her scores on tests involving picture interpretation were somewhat below normal, but not in the range typical for patients with RH strokes.

By this time she had begun to have hallucinations. In mid-October she reported seeing black spots before her eyes; by late October the black spots were described as insects climbing the walls. At this point she was still quite aware that the black spots were not in fact insects, remarking rather that they "looked like black bugs."

In mid-November, in view of increasing gait problems and increasing difficulties in activities of daily life, she was hospitalized in the Department of Neurology at the Ministerial Hospital of the Polish Ministry of Internal Affairs and Administration in Cracow. Her problems with naming increased to the point of anomia measurable on the BNT, and she was observed to have difficulties with pragmatics: inability to maintain the topic of conversation, violations of turn-taking rules, abrupt and unmotivated termination of conversations. The family, nursing staff and fellow patients reported an increasing tendency to monologize. When interviewed again by the present authors in early December she did not maintain eye contact with her interlocutor and frequently rambled off the subject. More and more often she left sentences unfinished, and when prompted to continue she reported that she did not remember

what she wanted to say.

By mid-December the patient had fallen into a state best characterized as hallucinosis, since she had lost criticism of her hallucinations, which had become much more frequent. During this period she showed for the first time a pathological score on the WAB, and verbal contact with the examiners began to be difficult, as she fell into mumbling and did not comply with instructions. When actively hallucinating she was highly agitated, disoriented and unresponsive. In view of the rapid 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. When the results of this test were returned positive in January 2001, the patient was given a clinical diagnosis of CJD. Genetic testing performed at the Institute of Neurogenerative Diseases at the University of California, San Francisco, under the supervision of Prof. Stanley Prusiner, has so far determined that the most common mutation responsible for the genetically transmitted variants of CJD (at codon 129) is not present; further investigations are in progress. Bacterial and viral encephalitis have been ruled out, as well as neoplastic 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 in clinical testing suggest the diagnosis of the rare Heidenhain variant of CJD (Heidenhain, 1929, Brazis et al., 2000).

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 (see Table 1 below). By this time the patient was bedridden with severe left hemiparesis; visually she reacted only to large, red objects, so the authors adapted a number of tests accordingly to enable her to complete the tasks. She recognized and correctly identified some of the large red cut-out figures, though her verbal output was now scarce and barely audible. A figure cancellation test for neglect using large red stars revealed left-sided hemispatial neglect. When asked to point to specified geometrical figures she was able to comply, though in order to look at the test cards she turned her head sharply to the right and rotated her eyes sharply to the left. In conversation she answered direct questions with a significant delay (1-5 seconds), using the minimum possible number of words.

By the end of December 2000 the patient was providing only one- or two-word answers to simple direct questions; when a more elaborate answer was demanded she responded only by shaking her head. Since in the Polish language it is normal to give an affirmative answer by repeating the verb used in the question, it is somewhat more difficult than in English to label her verbal behavior as echolalia, but in fact she seldom ventured an answer that was not contained in the question. She used only nouns in the nominative case (the Polish noun system is characterized by an elaborate inflectional system), and gradually began to slur, and then drop the inflectional endings on the verbs. At a certain point she began to answer questions by using the verb in the infinitive, which in Polish is considered characteristic of the speech of small children, foreigners, and the mentally retarded.

In early January, 2001, we were able to evoke no more than three or four words in simple repetition. Attempts to stimulate further speech production met with resistance: the patient 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 she was completely out of logical contact. By this point the myoclonus and hyperkinesia typical of advanced CJD had become very pronounced and nearly constant. She reacted to sudden noises by slowly raising her right arm after a 1-2 second delay. At such times she often displayed a catatonic reaction: the arm would remain in the position she left it, or in the position given by the therapist, until moved by some outside force. She had sleep-wake cycles and often held her eyes open during the day, but did not follow movements or show any sign of voluntary eyeball movement; a specialized ophthalmological examination showed cortical blindness with no remarkable ocular pathology. When open, her eyes moved in a constant symmetric jerking rhythm upward and to the left.

In view of the typical progress of the disease and the high probability that the diagnosis is accurate, there was a general expectation that death would ensue within the next few days or weeks. However, she has remained stable in the present condition since January 2001, with no significant changes. The hyperkinesia and myoclonus have receded, but not completely disappeared. The patient must now be fed by

TEST	Scale	Examination		
		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	100	75	45	9
Cracow Right Hemisphere Diagnostic Battery				
Agnosia	100	94	73	12
Constructive apraxia	100	87	41	3
Apragmatism	100	95	59	10
Perseveration	50	45	31	14

Table 1. Results of standard neuropsychological tests in October, November, and December, 2000 (from Pachalska et al., 2001a, reprinted with permission).

gastric tube, since the swallowing reflex has disappeared. Infections have developed on several occasions, but so far the organism, despite the weakened condition, has successfully defended itself.

3. Remarkable features

3.2. Agraphia as an early sign of incipient onset

Though there are several reports of aphasia as an initial presenting symptom of CJD in the literature (Cataldi et al., 2000; Hillis & Selnes, 1999), there is no previous mention of agraphia, which in the case here presented appears in retrospect to have been the first explicit neurological symptom. A careful examination of Fig. 1 will reveal that the patient's difficulties with writing are not simply the result of distorted vision; in this context the co-occurring perseveration and disorganization are especially revealing. Writing requires both a visual and motor image of the letters to be formed (Pachalska et al., 2001b; Brazis et al., 2000), and is thus somewhat more dependent on right-hemisphere functions than is speech. The particular nature of the patient's agraphic errors visible in Fig. 1 – esp. disorganization and lack of proportion – also argues for right-hemisphere involvement.

3.3. Linguistically-mediated progression from visual disorders to hallucinosis

The evolution of hallucinosis in this case is particularly interesting (Pachalska et al., 2001a). From the neurolinguistic perspective, the process that led from visual disorder to organic hallucinosis can be conceived as a language-driven progression: from "I see black spots on the wall," to "The black spots *look like* bugs," to "The black spots *are* bugs," to "There are black bugs climbing up the wall." That is, the pathological visual representation becomes a hallucination precisely at the point when it is named (Brown, 1988), while the crucial turn in the process consists in a metaphor that came to be confused with the concrete representation. In other words, the patient began by simply describing the visual phenomenon, being fully aware that the spots were not really there on the wall; this is in fact what prompted her to seek medical attention initially. Later, she used an analogy to describe the appearance of these black spots, but in time the analogy was transformed into a statement of fact. Yet later, the patient lost all criticism and interpreted what she was seeing literally, using the category suggested by the metaphor, at which point it would be proper to speak of "organic hallucinosis" (acc. to the ICD-10, cf. Heinz et al., 1995). Thus as a result of increasing anxiety coupled with the loss of critical faculties the patient made a gradual transition, mediated by linguistic interpretation, from visual disorder to active hallucination, which ended only when she completely lost logical contact with the environment.

3.3. Rapidly developing organic mutism

The results shown in Table 1 are remarkable for the very atypical time frame within which the neuropsychological parameters declined. This is neither sudden onset, as in the case of a stroke or traumatic brain injury, where ischemia or edema leads to necrosis in a matter of minutes or at most hours, nor is it the slow but steady decline typical of degenerative diseases, such as Alzheimer's Disease, where the development of symptoms may be a gradual process lasting several years. Indeed, the results shown in Table 1 would be typical for dementia of the Alzheimer type (DAT), if the successive tests were at intervals of one year, and not one month.

This pertains in a very particular way to organic mutism, defined here according to Lebrun (1990) as the absence of oral-verbal expression, along with neurological deficits suggesting CNS damage, in the absence of apparent 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 behavior as psychiatric 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.

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Samenvatting

In dit artikel wordt het optreden van mutisme beschreven bij een patiënte die lijdt aan de Heidenhain variante van de ziekte van Creutzfeldt-Jakob. Visuele stoornissen zijn doorgaans de eerste symptomen van deze variante. Bij de hier beschreven patiënte was de progressie van de eerste opgemerkte spraak- en taalafwijkingen tot het ver-

worven organische mutisme, continu en bijzonder snel. Het eerste symptoom bestond uit een dysgrafie (geïllustreerd in documenten daterend uit de zomer 2000), vervolgens traden progressieve visuele stoornissen op die uitmondden in hallucinaties. In de periode december-januari trad een zeer snelle neuro(psycho)logische deterioratie op (dementie) die leidde tot het mutisme. Wij bespreken de neurolinguïstische betekenis van onze bevindingen.

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