

# Creutzfeldt-Jakob disease in Sweden

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## Abstract

**Objectives**—To find and investigate, retrospectively, as many cases as possible of Creutzfeldt-Jakob disease (CJD) in Sweden dying during the period 1 January 1985 to 31 December 1996 and to detect any possible case(s) of new variant CJD.

**Methods**—The patients were found through computer search of all death certificates in Sweden on which CJD was mentioned, through information from the Swedish neuropathologists, and spontaneous reports from Swedish doctors and hospitals. Data concerning the patients were then collected from patients' case records and from brain histopathology reports.

**Results**—In total 72 cases of spongiform encephalopathy were confirmed as definite by neuropathology, one of them with Gerstmann-Sträussler-Scheinker disease. In 51 further cases there were no brain pathology data but the diagnosis "probable" (37 patients) or "possible" (14 patients) CJD according to WHO criteria could be made on clinical grounds. There was a variation in number of deaths/year, from a minimum of five (1985) to a maximum of 16 (1990). Sixty patients died during the period 1985-90 and 62 during 1991-6. The sex ratio was nearly 1:1. Calculated for a population of 8.6 million (mean of 12 years) in Sweden this gives 1.18/million/year. Age at the time of the presenting symptoms ranged from 34 to 84 years. Only one patient was under 40 at the onset of symptoms. He had a spongiform encephalopathy but prion protein staining was negative. The duration of symptoms that could be attributed to CJD was 6 months or less in 75 cases, 7-12 months in 16 cases, 1 to 2 years in 15 cases, and more than 2 years in 16 patients. By definition all patients were demented. Other more common symptoms and signs were aphasia, dysphasia, dysarthria, ataxia, myoclonus, pareses of the extremities, rigidity or spasticity, different types of hyperkinesias, and other psychiatric symptoms (depression, anxiety, and aggressiveness). Less common symptoms were hallucinations (mainly visual), visual defects, sensory symptoms (paraesthesias, itching, or pain), apraxia of swallowing, and disorders of eye movements.

**Conclusions**—The incidence, the symptomatology, the age distribution (age in years at onset and at death), and the duration of illness were similar to those of other countries except for the cases of new variant CJD in the United Kingdom.

## There is so far no indication of any cases of new variant CJD in Sweden.

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Keywords: Creutzfeldt-Jakob disease; prion disease; incidence; Sweden

In England and Wales a series of studies have attempted to identify all cases of Creutzfeldt-Jakob disease (CJD) since 1970 and in the whole of the United Kingdom this has been ongoing since 1985. Because of the bovine spongiform encephalopathy problem a prospective surveillance was instituted for the whole of the United Kingdom in 1990.<sup>1</sup> In France cases of CJD have been studied as far back as 1968 in collaboration with the Laboratory for CNS studies at the National Institute of Health.<sup>2,3</sup> In Germany and some other countries in the European Union cases of CJD have been investigated since 1993.<sup>4</sup> When the first report on a new variant (nvCJD) form of CJD with suspected connection with bovine spongiform encephalopathy appeared in March 1996,<sup>5</sup> the question was immediately (April 1996) raised at the National Board of Health and Welfare in Sweden. It was decided that Sweden should also institute a retrospective search and a prospective surveillance of all cases of CJD and cases of similar types in the country to try to find the "true" incidence of the disease in Sweden as well as to discover any cases of nvCJD. Only very few cases of CJD have up to now been published from this country<sup>6</sup> and very little was known about the occurrence of cases here. Because of the very strict patient secrecy regulations the study could only be accomplished as a scientific project. The author of this paper was commissioned to carry out the study as an independent researcher but in close collaboration with the Infectious Disease Control Unit at the National Board of Health and Welfare (Dr Peet Tüll), which also supported the study financially. After ethical approval the procedure was started in October 1996 and the last (latest) data, concerning a patient up to December 1996, appeared in March 1998. From March 1998 CJD became a notifiable disease in Sweden. The time period from January 1997 on will be covered later in an appropriate way by the Swedish Institute for Infectious Disease Control.

## Methods

Most patients were found through a computer search of all death certificates in Sweden on which CJD was mentioned during the actual period of time. These data are on file for the whole country at the Epidemiological Centre in Stockholm. Other sources were information

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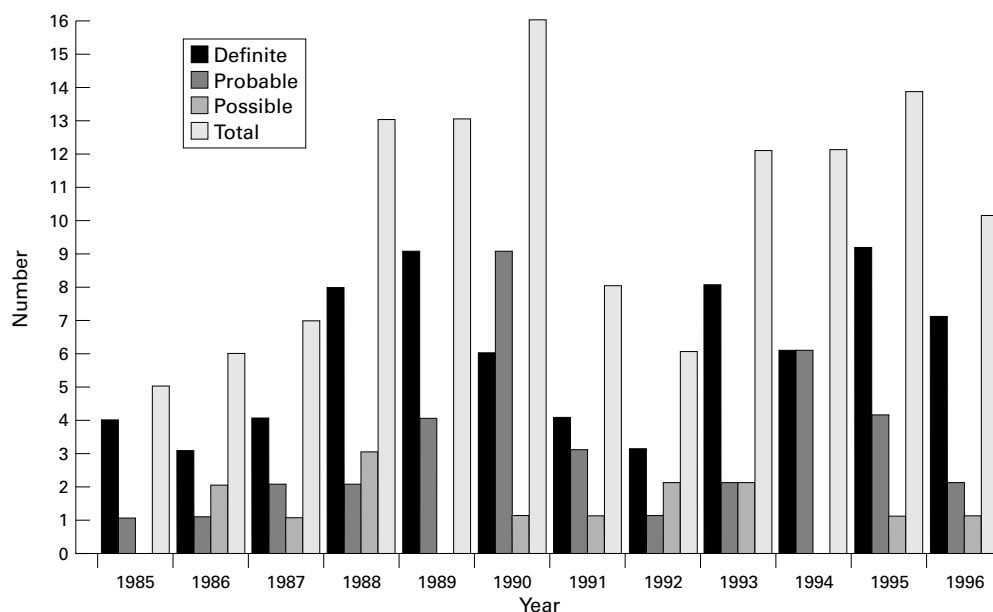


Figure 1 Number of deaths/year in cases of CJD in Sweden 1985-96.

from Swedish neuropathologists and spontaneous reports from Swedish physicians and hospitals. Data concerning the patients were then collected from hospital case records, from information given by general practitioners and others, and from brain histopathology reports. The physicians who had been responsible for the patients in question were informed by individual letters in each case. Equivocal neuropathological diagnoses were discussed at group meetings with the neuropathologists. The study was approved by the committee of ethics at the Uppsala Medical Faculty (Dnr 96/291).

### Results

In 72 cases the diagnosis of spongiform encephalopathy was confirmed as definite by neuropathology. In one of these the diagnosis of Gerstmann-Sträussler-Scheinker disease was established. In 51 further cases there were no brain pathology data but the diagnosis "probable" (37 patients) or "possible" (14 patients) CJD according to WHO criteria<sup>7</sup> (see also Kretschmar *et al*<sup>8</sup>) could be made on clinical grounds (table 1). The material thus includes in total 123 cases. Data from all except the patient with Gerstmann-Sträussler-Scheinker disease (62 men and 60 women) are presented.

Table 1 Clinical diagnostic criteria for CJD according to WHO<sup>7</sup>

|  |
|--|
| Definite CJD   |
| Neuropathology   |
| Probable CJD   |
| (1) Progressive dementia   |
| (2) Typical EEG (generalised triphasic periodic complexes at approximative 1 Hz) |
| (3) At least two out of the following:   |
| Myoclonus  |
| Visual or cerebellar disturbances  |
| Pyramidal/extrapyramidal dysfunction   |
| Akinetic mutism  |
| Possible CJD   |
| (1) Same clinical criteria as above  |
| (2) No EEG available or without a typical EEG                                    |
| (3) Duration less than 2 years   |

In 20 of the patients with definite and one with probable CJD the diagnosis or suspicion of CJD was not mentioned on the death certificates. In these cases the main diagnosis on the death certificates were dementia (four cases), progressive neurological disorder (four), brain disorder (three), Alzheimer's disease (two), atrophy cerebri (two), progressive encephalopathy (one), progressive supranuclear palsy (one), seizure disorder (one), viral encephalitis (one), and no diagnosis (two).

The cases had an uneven distribution over Sweden with a tendency to clustering. The incidence figures were three times higher in certain counties in the southern part of the country compared with the four most northern counties. However, the regional breakdown is not presented because of high risk of bias and low statistical power.

There was a variation in number of deaths/year, from a minimum of five (1985) to a maximum of 16 (1990). Sixty patients died during the period 1985-90 and 62 during 1991-6 (fig 1).

Calculated for a population of 8.6 million (mean of 12 years) in Sweden this gives 1.18 per million/year. If the Swedish figures are compared with other figures from the European Union, by definition only definite and

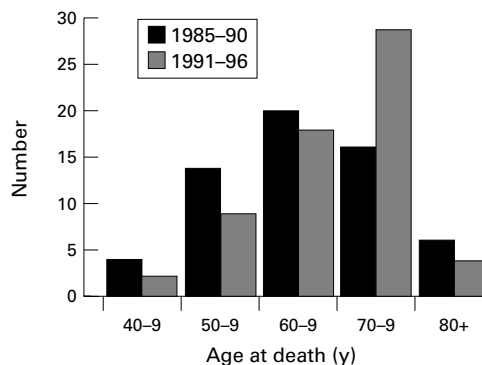


Figure 2 Age at death in 1985-90 and in 1991-96.

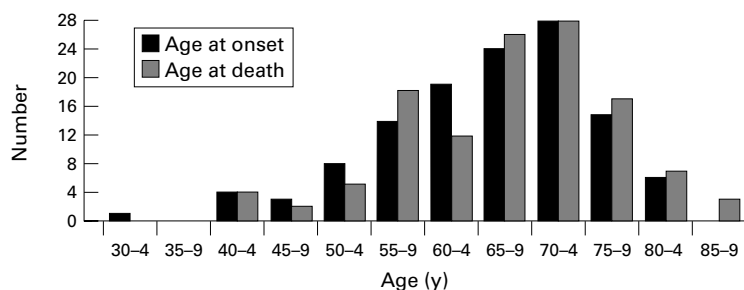


Figure 3 Age at onset and age at death in Swedish cases of CJD 1985-96.

probable cases should be included. In table 2 data from the years 1993-6 are shown in this way.

The time period was divided into two parts. During the first half, 1985-90, the mean age at death was 65.9 years and 18 of the patients (30%) were younger than 60 at the time of death. The corresponding figures for the second period, 1991-6, was 68.9 years and only 11 patients (17.7%) were younger than 60. No patient died before the age of 40 (fig 2).

Age at the time of presenting symptoms was 34 to 84 years (fig 3). One patient was under 40 at the onset of symptoms. This patient is described in detail.

He was born in December 1948. His grandmother was severely demented, the sister of his mother had an intracerebral arterial aneurysm and a brain tumour, and his mother was mentally ill. At 34 years of age he began to have difficulty in expressing himself, he had difficulty in spelling, became increasingly timid, and he lost his memory. He drove his car into other stationary cars and into the wall of his garage. Dysathria and a tongue deviation to the right was noticed and he had difficulty in following objects with his eyes. Later he did not talk at all. The progress was at first very rapid. Later he was found to have many primitive reflexes and a positive Babinski's sign. The case history does

Table 2 Incidence of CJD/year/million inhabitants in some European countries (France, Germany, Italy, The Netherlands, United Kingdom, and Sweden). Definite and probable CJD cases according to WHO criteria

|      | F    | D    | I    | NL   | GB    | S    |
|------|------|------|------|------|-------|------|
| 1993 | 0.78 | 0.65 | 0.54 | 0.87 | 0.78  | 1.15 |
| 1994 | 1.04 | 0.76 | 0.53 | 1.0  | 1.02  | 1.40 |
| 1995 | 1.07 | 0.98 | 0.00 | 0.4  | 0.77  | 1.48 |
| 1996 | 0.00 | 0.87 | 0.00 | 0.00 | 0.75* | 1.02 |

\* Data from Cousens *et al.*<sup>1</sup> Swedish data from the present study. Other data are from EU BIOMED Program "Surveillance of Creutzfeldt-Jakob Disease in the European Community" according to Poser *et al.*<sup>4</sup>

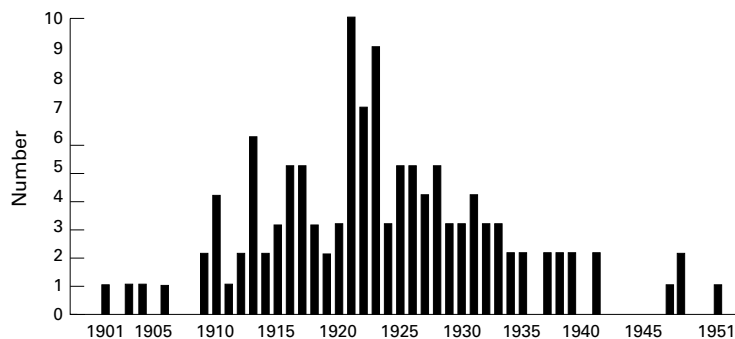


Figure 4 Years of birth of 122 Swedish cases of CJD.

not contain any mention of myoclonus, ataxia, or Parkinson-like symptoms. Brain CT one year after the onset of the symptoms was normal and one year later showed a slight cortical atrophy. Three electroencephalograms were obtained 1 and 2 years after the onset and showed nothing abnormal. He eventually died of bronchopneumonia in 1988 at 40 years of age. Histopathology of the brain (performed by Dr Arne Bruhn) showed the following: pronounced spongiform degeneration within the cerebral cortex with loss of neurons but only a discrete gliosis. Pronounced changes also occurred in the nucleus caudatus and putamen. The substantia nigra was almost totally destroyed and contained only a few pigmented neurons. Only discrete changes were seen in the cerebellum. Immunohistochemistry for prion protein at two different laboratories was negative in all areas. From the neuropathological point of view this was judged to be a case of spongiform encephalopathy and nigrostriatal degeneration.

Figure 4 shows the distribution of years of birth. Most of the patients were born in the 1920s with a maximum between 1920 and 23. No patient was born after 1951.

The duration of symptoms that could be attributed to CJD was 6 months or less in 75 patients, 7-12 months in 16 patients, 1 to 2 years in 15 patients, and more than 2 years in 16 patients (fig 5). Seven of these 16 patients had typical neuropathology, the other nine were not necropsied. The onset of the symptoms was rather abrupt in 86 of the patients and slower in the other 36. In 55 of the 86 patients the symptoms started during the months of January to June (18 in January) and only 31 during the second half of the year.

By definition all patients were demented (table 3). Seventy two patients had other psychiatric symptoms, such as depression, anxiety, and aggressiveness. Ninety seven patients had ataxia and 110 aphasia, dysphasia, and dysathria. Ninety patients had myoclonus and 65 other types of hyperkinesias, mainly tremor and chorea. Rigidity or spasticity was mentioned among 75 patients. Eighty patients had limb pareses or reflex abnormalities. A combination of typical amyotrophic lateral sclerosis and CJD was seen in one patient. One further patient had had signs of polyneuropathy for some 10 years before the onset of the CJD. Less common symptoms were hallucinations (mainly visual, 30 cases), visual defects (22 cases), sensory symptoms (paraesthesias, itching, or pain, 19 cases), difficulties in swallowing (mainly apraxia of swallowing, 38 cases) and disorders of eye movements (34 cases). Sensory symptoms were more common among younger patients and hallucinations among older patients. Any of the symptoms mentioned appeared at onset. However, most often dementia or ataxia were the presenting symptoms (table 4). In 14 cases the initial symptoms were described in the case histories as "functional" or "hysterical".

The symptoms in the definite group (n=71) compared with the probable+possible group (n=51) were similar. Thus 67% in both groups

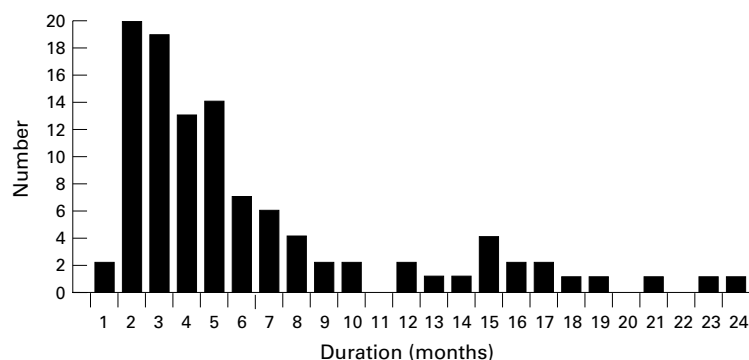


Figure 5 One hundred and six Swedish cases of CJD with a duration <2 years.

had memory defects, 73% had myoclonus, and 82% had aphasia and apraxia. Disorientation was slightly more common in the definite group (86% *v* 70%), as well as ataxia (85% and 73% respectively) and signs of pyramidal tract involvement (70% and 59% respectively). These data indicate a similar brain dysfunction in the patients with probable or possible CJD compared with those with definite CJD.

Between one and seven EEGs had been recorded from 119 of the 122 patients. Out of the 71 patients with a definite diagnosis only 42 had EEG changes typical for CJD (generalised triphasic periodic complexes at about 1 Hz). In the other 29 cases the EEGs were either not recorded, were normal or showed non-specific changes. Epileptic seizures or epileptiform activity on EEG was seen in 45 of the 122 patients. Brain CT was carried out once or more in 115 of the patients and one MRI was carried out in 45 of the cases. Neither of these methods showed any particular changes. In some cases slight brain atrophy was seen as well as some non-specific MRI changes in white matter on T2 weighted images. In none of the patients were any high signals on T2 weighted images seen in the posterior thalamus.

The case records on heredity were often incomplete. In 10 cases (8%), including the patients with an onset of symptoms at the age of 34, it was recorded that a close relative had symptoms of dementia at an old age and in five cases Parkinson's disease was mentioned in the family history. Unfortunately no DNA studies have been done. There were no indications of a common hereditary pattern among the patients. However, a genealogical study is planned. The case of Gerstmann-Stäussler-Scheinker disease is not included in this

Table 3 Clinical symptoms and signs in 122 Swedish patients with CJD dying 1985-96.

|                               |                        |
|-------------------------------|------------------------|
| Dementia                      | 122 (71) by definition |
| Aphasia/apraxia               | 112 (58)               |
| Ataxia                        | 97 (60)                |
| Myoclonus                     | 91 (53)                |
| Paresis                       | 80 (50)                |
| Rigidity/spasticity           | 75 (47)                |
| Anxiety/depression/aggression | 72 (42)                |
| Tremor/chorea                 | 65 (33)                |
| Difficulty in swallowing      | 39 (22)                |
| Disorders of eye motility     | 34 (25)                |
| Epileptic seizures            | 34 (21)                |
| Hallucinations                | 30 (14)                |
| Visual defects                | 22 (13)                |
| Sensory symptoms              | 19 (11)                |

Figures in parentheses are cases verified by neuropathology

Table 4 Presenting symptoms or signs in 122 Swedish patients with CJD 1985-96. Most common combination of symptoms and signs was dementia and ataxia (17 patients)

| Symptom/sign           | n  |
|------------------------|----|
| Dementia               | 61 |
| Ataxia/vertigo         | 48 |
| Aphasia/apraxia        | 10 |
| Paresis of extremities | 7  |
| Depression             | 6  |
| Sensory                | 4  |
| Oculomotor             | 3  |
| Rigidity/tremor        | 3  |
| Visual                 | 2  |
| Myoclonus              | 2  |

presentation but so far no other case of spongiform encephalopathy is known in any of the families.

## Discussion

### COMPARISON WITH OTHER LARGE NATIONAL SERIES

A study of 230 consecutive cases of neuropathologically verified cases of CJD in France from 1 January 1968 to 31 December 1982 gave a female/male sex ratio of 1.2/1.<sup>9</sup> Twenty seven patients were under the age of 50 (11.7%) at the onset of the disease.

During the period 1992-5 216 cases of CJD were ascertained in France through a national network of neurological departments and neuropathological laboratories. Seventy two cases were definite, 103 probable, and 41 possible, equal to an incidence of 0.87/million inhabitants. The female/male sex ratio was 1.18.<sup>10</sup>

An analysis of death certificate information in the United States for 1979-90 from the National Center for Health Statistics gave 2614 deaths (female/male sex ratio 1.13) with CJD listed on the death certificates. The average annual age adjusted mortality was 0.9/million persons. Only 112 persons (4.3%) were under 50 years of age at death.<sup>11</sup>

In both these studies there was an uneven distribution of cases of CJD over the countries.<sup>10 11</sup>

An epidemiological surveillance for CJD was carried out in England and Wales from 1970 to 1984 and for the whole of the United Kingdom during 1985-96.<sup>1</sup> The cases were established from referral of suspected cases by neurologists, neuropathologists, and neurophysiologists and from death certificates. Definite and probable cases were included; 662 patients were identified as sporadic cases of CJD. Fifty two patients (7.9%) were under 50 years of age. There were slightly more women than men.

The total number of neuropathologically detected cases of CJD in Austria from 1969 until 30 September 1995 was 79, with a female/male ratio of 1.14/1.<sup>12</sup> Four of the patients (5%) were under 50 years of age at death.

In the present Swedish study (1985-96) 108 definite and probable cases of CJD were found. Six patients (5.5%) of these 108 were under the age of 50 at time of death. The female/male ratio was 0.86/1. For the total of 122 cases, which includes possible cases, the sex ratio was almost 1/1.

Between 1 June 1993 and 21 April 1997 (3 years and 10 months) 232 definite or probable cases of CJD were found in Germany by the use of a voluntary reporting system.<sup>4</sup> Only six cases (2.5%) were under the age of 50 at the onset of symptoms. The female/male ratio was 2/1.

Symptomatology and age distribution of onset, death, and duration are very similar in all seven studies mentioned above. However, for unknown reasons the sex ratio in the German study showed a much higher proportion of females.

It is an interesting finding that in the present study the mean age at death was 66 years during the first 6 year period and 69 during the second 6 year period. There was no increase in total incidence when these two groups were compared but a clear increase in the age group 70–79. Most of the patients in the present series were born in the 1920s. An increase over the years of patients with CJD older than 70 has also been found by others.<sup>1–10</sup> In a study of French patients from 1968–77 the mean age was 60 years at onset with a mean duration of illness of 8.5 months.<sup>3</sup> The explanation is unknown but it might reflect some kind of mechanism in the development of sporadic CJD many years back in the histories of the patients. However, it is probably the result of more elaborated diagnostic procedures in older persons currently.

#### SHOULD CASES OTHER THAN “DEFINITE” OR “PROBABLE” BE INCLUDED?

According to the WHO criteria a case could be classified as possible if it did not fulfill the EEG criteria but fulfilled the clinical criteria and had a clinical course <2 years.

The course of the illness in CJD is usually short. However, in large series there are some verified cases of long duration. Thus, Brown *et al.*<sup>13</sup> found 33 cases out of 357 (9%) of histopathologically verified cases and 17 out of 225 (7%) verified by transmission with a clinical course that extended for 2 years or more. The longest transmitted case had a duration of 13 years. In the present series seven out of 71 (10%) definite cases (histopathologically verified) had a duration of more than 2 years and the longest duration for a definite case was 8 years. Thus, a long duration does not exclude the possibility of the diagnosis of CJD.

#### ACCURACY AND RELIABILITY OF EEG CHANGES IN CJD

In a blinded study of EEGs in 15 patients with neuropathologically confirmed CJD and 14 patients with other types of dementia periodic sharp wave complexes were found with a sensitivity of 67% and a specificity of 86%.<sup>14</sup> The figures in other studies vary a great deal. In the present study only 42 (59%) out of 71 histopathologically verified patients had typical EEG changes. However, this was a retrospective study and the EEGs were analysed by many different interpreters not using very strict criteria. In a retrospective study not much can be done to increase the reliability of the neuro-

physiology as no further EEGs could be taken and sometimes no EEG curves could be recovered.

Thus to use typical EEG changes as a criterion for CJD in a retrospective study based on case records is not very suitable. In a retrospective study inclusion of not only the definite and the probable cases but also the possible cases reflects the “true” incidence of CJD better than just including “definite” and “probable” cases. However, in a prospective study a normal or non-specific EEG should always be followed by another EEG.

#### THE 34 YEAR OLD PATIENT

According to WHO criteria the 34 year old patient should be included as a definite case. However, immunohistochemistry for prion protein measured at laboratories with expertise in this technique was negative. It does not seem correct to exclude him from a series intended to estimate the incidence of CJD in Sweden as in no other case was immunohistochemistry done. Clinically, he was similar to the other patients with CJD, but the onset was early and the progress was rapid at first but then protracted. In his case there was heredity for dementia. It was certainly not a case of Gerstmann-Sträussler-Scheinker disease nor of fatal familiar insomnia. It is well known that the onset of the disease as well as the rate of progress is different in hereditary cases of CJD compared with sporadic ones.<sup>15</sup> Because prion protein immunohistochemistry is a recent method we do not know how many sporadic cases of CJD published in the literature that were actually prion protein positive. Spongiform encephalopathy may be secondary to other mechanisms, but this case may also represent a new disease. The relatives of the patient will be further investigated.

#### NEW VARIANT CJD

Through systematic surveillance of CJD in the United Kingdom since May 1990 a new variant of CJD was described in 10 cases up to 1996.<sup>5</sup> Until September, 1997 21 such cases had been diagnosed in the United Kingdom<sup>16</sup> and one in France.<sup>17</sup> For 14 of these cases neurological<sup>16</sup> and psychiatric<sup>18</sup> features have been described in detail. Eight of the 14 patients were women. The mean age of onset was 29 (range 16–48) years and the median duration of the illness was 14 (range 9–35) months which is two to three times longer than for sporadic CJD cases defined as above. All of these patients had early psychiatric symptoms and eight patients had early sensory symptoms. Ataxia and some form of involuntary movements developed in all cases and seven of them had myoclonus. The EEG was abnormal in 12 of the patients but typical 1 Hz periodic complexes were not seen in any case. Neuropathological studies,<sup>5</sup> and molecular analysis of prion protein strain variations<sup>19</sup> as well as experiments on transmission to mice<sup>20</sup> have established this as a new variant of CJD (nvCJD).

## NEW VARIANT CJD WAS NOT FOUND IN SWEDEN

One of the main purposes of the present investigation was to ascertain if there were any nvCJD cases in Sweden. So far cases of nvCJD have not been identified outside the United Kingdom and France. The suspicion that nvCJD could be linked to bovine spongiform encephalopathy in cattle is the main reason behind the framing of such a question. Because bovine spongiform encephalopathy was originally supposed to have first appeared in 1985, this became the year of onset for the present retrospective surveillance. The main clinical characteristic of nvCJD is young age. One man in the present study was 34 years of age at onset and five further patients (two men and three women) were under 49 (range 40–46) at onset. All six except the oldest one were definite cases with a neuropathology typical for sporadic CJD. However, typical EEG changes were only seen in one of them, and the duration varied between 6 months and 2.7 months. There is no information on sensory symptoms in any of these six patients. Such symptoms are declared characteristic for cases of nvCJD by contrast with sporadic CJD.<sup>16</sup> The symptomatology and course of the illness among the six young patients in the present study were very similar to what has been published for other young cases of sporadic CJD.<sup>13 21–23</sup> The duration of the illness seems to be considerably longer in younger patients than in most older patients.

There is no indication that any of the Swedish cases were iatrogenic. Iatrogenic cases are usually younger (most of them being growth hormone recipients). It cannot be excluded that one or more of the six younger patients had a familiar form of CJD. However, no data supporting this possibility exist so far. Thus the six younger CJD patients are considered as sporadic CJD cases but further investigations will be made.

### Conclusions

When compared with other large international series from the United States, the United Kingdom, France, and Austria the following conclusions can be drawn: The incidence seems to be similar to that seen in later years in other countries (around 1/million/year). The age distribution (age at onset and at death) and the duration of illness are similar to those of other countries except for the nvCJD cases in the United Kingdom. The symptomatology is similar as far as can be judged. There is so far no indication of any nvCJD cases in Sweden.

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