Epidemiological Report

Creutzfeldt-Jakob Disease and other prion diseases
Historic Series 2010 – 2021

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CREUTZFELDT-JAKOB DISEASE

Prion diseases represent a group of rare, invariably fatal neurodegenerative diseases that occur in both humans and animals and can be transmissible or hereditary. They are also called transmissible spongiform encephalopathies (TSEs) due to the microscopic findings on anatomopathological examination, which include vacuoles in the brain tissue.

In humans, the most common of them is Creutzfeldt-Jakob disease (CJD),¹ with an incidence of one case per million inhabitants per year. With a low prevalence, it is characterized by rapidly progressive dementia associated with other signs and symptoms, most often affecting people between 50 and 70 years of age and reaching a severe stage in a few months. It is always fatal and there is no treatment.²

The CJD has been known for a long time, but it only acquired importance in public health due to the emergence of the new form related to the consumption of meat contaminated with bovine spongiform encephalopathy (BSE), popularly called “mad cow disease”, after the cattle epidemic in the UK in the mid-1980s. The first human cases of the dietary form appeared in 1996, called variant CJD (vCJD), with clinical-pathological and laboratory characteristics, associated with the consumption of meat from cattle with BSE.

The vCJD, unlike the classic form, predominantly affected young people, below 30 years of age. It has an atypical symptoms, prominent early psychiatric or sensory symptoms, and late neurologic abnormalities (approximately six months to two years after the psychiatric symptoms) (Chart 1).

### Chart 1. Clinical, epidemiological and neuropathological features of CJD and vCJD.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Transmission mode</th>
<th>Clinical condition</th>
<th>Affected groups</th>
<th>Onset of symptoms/ evolution</th>
<th>Neuropathological changes</th>
<th>CMR EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CJD</td>
<td>Sporadic - undetermined</td>
<td>Early dementia Myoclonus Pyramidal/ extrapyramidal and cerebellar signs</td>
<td>Men and women (one case/ million people/ year)</td>
<td>50-70 years 1 year (average 8 months)</td>
<td>Prion plaques - vacuoles in subcortical gray matter/cerebral and cerebellar cortex</td>
<td>Hypersignal in caudate and putamen (60%) Typical (70%)</td>
</tr>
<tr>
<td>CJD</td>
<td>Familial - mutations in protein genes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CJD</td>
<td>Iatrogenic – acquired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vCJD</td>
<td>Acquired - Prion contaminated meat</td>
<td>Early dementia Myoclonus Pyramidal/ extrapyramidal and cerebellar signs</td>
<td>Men and women</td>
<td>under 30 years 6 months to 2 years (average 13 months)</td>
<td>Deposits of prion plaques surrounded by a halo of vacuoles spongiform “Florid” plaques</td>
<td>Thalamus (pulvinar sign) - 90% Typical - 0%</td>
</tr>
<tr>
<td>vCJD</td>
<td>EBB - Blood transfusion</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Source: Adapted from WHO (2003).¹
As a resource for the detection of this new form of transmission, the World Health Organization (WHO) proposed, from 1998, global sentinel surveillance of prion diseases, with emphasis on CJD, establishing standardized criteria for definition, classification of cases and diagnostic tests. In the state of São Paulo (SSP), a retrospective study of CJD cases, based on hospital admissions (AIH) and deaths (Fundação Seade), outlined the profile of the disease between 1990 and 2001. Thus, sentinel surveillance was initiated in 2000, with the preparation of the investigation form and the integration with neurology services and laboratory references.

In 2005, CJD was included in the National List of Notifiable Diseases and was incorporated into the Notifiable Diseases Information System (Sinan). However, without own form yet, the case is recorded on a individual notification/conclusion module and another form, more complete, specific to Prion disease, with all necessary informations about the case, is filled out and sent to the Division of Food and Waterborne Diseases/Epidemiological Surveillance "Prof. Alexandre Vranjac"(DFWD/ESC).

CLASSIFICATION OF CJD CASES

- **Possible:**
  - Progressive dementia;
  - duration of symptoms less than two years until death; and
  - at least two of the following clinical features: myoclonus, visual or cerebellar disorder, pyramidal/extrapyramidal dysfunction, akinetic mutism

- **Probable:** (in the absence of an alternative diagnosis)
  - Progressive dementia;
  - at least two of four clinical features: myoclonus, visual or cerebellar disorder, pyramidal/extrapyramidal dysfunction, akinetic mutism; and
  - electroencephalogram (EEG) characteristic of the disease and/or magnetic resonance imaging of the skull with characteristic changes and/or positive CSF for protein 14-3-3 and clinical duration of less than two years until death.
• Defined case
  o Neuropathological confirmation after death and necropsy and/or
  o confirmation of protease-resistant prion protein (immunocytochemistry) and/or
  o presence of mutation in the prion protein gene in familial CJD.

• Inaccurate case
  o When the criteria for possible, probable or confirmed are not met and there is no reasonable alternative hypothesis, and the diagnosis cannot be ruled out.

CLASSIFICATION OF vCJD CASES

The new variant (vCJD) also follows its own criteria for classifying cases.

• Possible vCJD
  o Clinical condition with early psychiatric symptoms;
  o painful dysesthesias, ataxia, myoclonus, late dementia;
  o duration greater than six months; and
  o no evidence of alternative diagnoses, iatrogenic exposure, or familial form.

• Probable vCJD
  o The above features plus electroencephalographic features not typical of CJD; and
  o CMR with pulvinar hypersignal and/or tonsil biopsy with immunohistochemistry demonstrating the presence of abnormal prion protein (PrP).

• Defined vCJD
  o Neuropathological examination showing, in addition to spongiform alterations, PrP deposition with a characteristic appearance of “florid plaques” in the brain and cerebellum.
ETIOLOGICAL AGENT – THE PRION

The etiologic agent is an abnormal isomer of the glycoprotein known as the cellular prion protein. Present in neurons, after undergoing a modification it assumes the pathogenic form called proteinaceous infectious particles (prion). These protein molecules have a tropism for neural tissue; and are highly stable and resistant to freezing, drying, heat from normal cooking, pasteurization and sterilization at the usual temperature and time. They are resistant to gastrointestinal proteases, low pH, ultraviolet radiation, ultrasonic energy, ionizing radiation and most disinfectants.

Even without having DNA, they multiply quickly due to the ability to interact with cellular prion protein molecules and convert them into pathogens, simply by changing their spatial structure.

TRANSMISSION MODE

There is no person-to-person transmission, through sexual contact, saliva, feces, urine or other body fluids (except cerebrospinal fluid). Clinical, social and non-invasive clinical investigations, diagnostic tests and interventions involving non-infectious tissues with TSE patients pose no risk to healthcare workers, relatives or the community.\footnote{1}

In most patients, CJD occurs as a random disease with no recognizable pattern of transmission (Sporadic CJD). A smaller proportion of patients develop CJD due to inherited mutations in prion protein genes (Familial CJD). Others have a iatrogenic origin, associated with the agent transmission through use growth hormones, dura mater grafts, neurosurgical instruments or corneal transplantation from prion-carriers donors (iatrogenic CJD). The following human tissues are considered infective: brain tissue, spinal cord, eyes, lymph nodes, tonsils, dura mater, pineal gland, placenta, cerebrospinal fluid, pituitary and adrenal.\footnote{2}

The vCJD, by foodborne transmission, is called acquired form.

EPIDEMIOLOGICAL SITUATION

When analyzing the years from 2010 to 2021, there are 426 suspect cases notified, of which 231 (52.4%) were diagnosed with prion disease. The average in the period evaluated was 19.7 per year, with 2012 being the year with the highest number of suspected cases (38), followed by 2014, with 33 notifications (Graph 1).
Among those confirmed, 19% were classified as possible CJD, 72% probable and 8% defined by neuropathological examination of the brain or by finding a mutation in the cellular prion protein gene in the genetic analysis. In São Paulo, as of 2018, notifications have been concluded as possible or probable CJD, as there are no more state technical references for genetic and neuropathological analysis. For a better conclusion, it is necessary to have these references, because, in their unavailability, there is no way to conclude the diagnosis of defined or familial Creutzfeldt-Jakob Disease. If there are suspected cases of vCJD or others which require more detailed analysis, the material collected can be sent to the national reference, the Instituto Estadual do Cérebro Paulo Niemeyer (IEC), for neuropathological and immunohistochemical examinations.5

In the 22 years of existence of sentinel surveillance of prion diseases in the SSP and 17 years in Brazil, no suspected case of vCJD has ever been identified.

The average age of patients was 61 years and the age group with the highest volume of confirmed cases being between 50 and 59 years old (Graph 2).
Graph 2. Frequency in percentage of CJD cases according to age group, SSP, 2010 to 2021.*

By gender, 52% occurred in females (Graph 3).

Graph 3. Frequency in percentage of CJD cases according to sex, SSP, 2010 to 2021.*

According to the WHO, the incidence of CJD is one case per million inhabitants per year, which would result in the SSP in approximately 40 records per year.

To calculate the incidence, cases residing outside the territory of São Paulo were excluded and population data from the Fundação Seade – State System of Data Analysis for the years 2010, 2015, 2020 were used. The rates observed in the SSP, calculated per year, ranged from 0.16 to 0.87 cases per million inhabitants (Table 1).

Table 1. CJD incidence rate per 1 million population, SSP, 2010 to 2021.*

<table>
<thead>
<tr>
<th>Year</th>
<th>Nº of cases</th>
<th>Incidence/1,000,000 inhabitants</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>15</td>
<td>0.36</td>
</tr>
<tr>
<td>2011</td>
<td>14</td>
<td>0.34</td>
</tr>
<tr>
<td>2012</td>
<td>36</td>
<td>0.87</td>
</tr>
<tr>
<td>2013</td>
<td>32</td>
<td>0.77</td>
</tr>
<tr>
<td>2014</td>
<td>32</td>
<td>0.77</td>
</tr>
<tr>
<td>2015</td>
<td>14</td>
<td>0.32</td>
</tr>
<tr>
<td>2016</td>
<td>20</td>
<td>0.46</td>
</tr>
<tr>
<td>2017</td>
<td>20</td>
<td>0.46</td>
</tr>
<tr>
<td>2018</td>
<td>17</td>
<td>0.39</td>
</tr>
<tr>
<td>2019</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td>2020</td>
<td>7</td>
<td>0.16</td>
</tr>
<tr>
<td>2021</td>
<td>9</td>
<td>0.2</td>
</tr>
</tbody>
</table>


The average incidence rate found (0.45) is far below that described by the WHO and recorded in the literature, demonstrating that these diseases are possibly underreported.

The year 2012 was the one with the highest incidence (0.87/1,000,000 inhabitants) and 2021, with the lowest (0.2/1,000,000 inhabitants). When observing the distribution of reported cases in the period from 2010 to 2021, the city of São Paulo presented the highest volume of occurrences with a confirmed diagnosis of CJD (148 records) (Figure 1).
Through the genetic analysis performed, it was possible to diagnose, in addition to the familial forms of CJD, two cases of Gerstmann-Sträussler-Scheinker disease (GSS) and one of fatal familial insomnia (FFI), hereditary diseases also caused by prions (Table 2).
Table 2. Prion disease cases reported according to final diagnosis, SSP, 2010 to 2021.*

<table>
<thead>
<tr>
<th>Final diagnosis of cases reported as suspicious for CJD</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFINED CJD (NEUROPATHOLOGICAL OR PRESENCE OF MUTATION)</td>
<td>17</td>
</tr>
<tr>
<td>GSS</td>
<td>2</td>
</tr>
<tr>
<td>IFF</td>
<td>1</td>
</tr>
<tr>
<td>POSSIBLE CJD</td>
<td>46</td>
</tr>
<tr>
<td>PROBABLE CJD</td>
<td>168</td>
</tr>
<tr>
<td>DISCARDED (OTHER DIAGNOSIS/CLINICAL CONDITION DOES NOT CORRESPOND TO THE DEFINITION OF THE CASE)</td>
<td>29</td>
</tr>
<tr>
<td>FINAL DIAGNOSIS IGNORED (INACCURATE, INCOMPLETE OR BLANK NOTIFICATION)</td>
<td>163</td>
</tr>
<tr>
<td>TOTAL NOTIFICATIONS</td>
<td>426</td>
</tr>
</tbody>
</table>


According to the case definition, the duration of signs and symptoms until death is less than two years. In the notified cases, the survival after diagnosis, from the date of onset of symptoms to death, ranged from 16 days to 192 months. The median survival was 16 months. Among the reported cases diagnosed with CJD, it is stated that the most frequent reported symptom was progressive dementia, being present in 99.1% of cases, followed by psychiatric disorders (61%) and cerebellar disorders (43.7%) (Graph 4).

Graph 4. Frequency in percentage of the occurrence of signs and symptoms in cases diagnosed as CJD, SSP, 2010 to 2021.*

REFERENCES


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