Rev Bras Neurol 56(3):25-28, 2020.

Historical note

Creutzfeldt-Jakob disease: one hundred years of participation in the design of the transmissible spongiform encephalopathies

Doença de Creutzfeldt-Jakob: cem anos de participação no desenho das encefalopatias espongiformes transmissíveis

M. da Mota Gomes 1

ABSTRACT

Creutzfeldt and Jakob's disease (CJD) has its initial milestone in the publication issued 100 years ago that precipitated its better clinical-pathological and etiological understanding. Now, it is established that it belongs to the group of the prion diseases or transmissible spongiform encephalopathies family. CJD is itself divided into several types, the most common being sporadic that is further subdivided according to the anatomoclinical expression, but mainly due to its aetiology regarding prionic protein or genotype.

Key words- Creutzfeldt-Jakob disease, spongiform encephalopathies, prion protein

RESUMO

A doença de Creutzfeldt e Jakob (CJD) tem seu marco inicial na publicação emitida há 100 anos que precipitou seu melhor entendimento clínico-patológico e etiológico. Agora, está estabelecido que pertence ao grupo da família das doenças de príons ou encefalopatias espongiformes transmissíveis. A própria CJD se divide em vários tipos, sendo o mais comum o esporádico que também se subdivide de acordo com a expressão anatomoclínica, mas principalmente devido à sua etiologia em relação à proteína priônica ou genótipo.

Palavras-chave- Doença de Creutzfeldt-Jakob, encefalopatias espongiformes, proteína prioníca

Associate Professor, Laboratory of History of Psychiatry, Neurology, and Mental Health. Institute of Psychiatry. Institute of Neurology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil Orcid: https://orcid.org/0000-0001-8889-2573

Corresponding author: mmotagomes@acd.ufrj.br

INTRODUCTION

One hundred years ago, a paper was published. It inaugurated the process of recognition of the clinicopathological configuration of a new fatal and peculiar disease, one of the spongiform encephalopathies. That disease, nowadays known as Creutzfeldt-Jakob disease (CJD), is characterized by rapidly progressive dementia, frequently associated with behavioural and visual disturbances, ataxia, extrapyramidal features and myoclonus [7]. Many years passed before the definition of its aetiology, and complete configuration assigned it as one of the most prevalent human prion diseases[1].

This article is published to honour the centenary of that publication, by Hans Gerhard Creutzfeldt, in 1920, which details what supposedly would be the first case of sporadic CJD (sCJD).

RECOGNITION OF A NEW DISEASE

Hans Gerhard Creutzfeldt took the vanguard of the new disease definition for the reasons that follow. From 1912 to1914, he worked with Alois Alzheimer at the University of Breslau, and at World War I (1914–1919), he was a German naval medical officer. Afterwards, from 1919-20, he worked with Walther Spielmeyer in the Psychiatry Research Institute in Munich, but soon he moved to the Charité Hospital in Berlin, where he worked with Karl Bonhoeffer. After 14 years, he returned to Kiel in 1938 to become rector of the psychiatry and neurology clinic at the Christian-Albrechts University (1938–1945). He then worked until retirement in 1955 at the Institute of Psychiatry, Munich[8,4]. Despite the environment at the time of Nazi hegemony, Creutzfeldt has never been a member of the National Socialist Party. He did not act in the interest of the regime; on the contrary, he prevented patients considered a burden for the state to be killed in the Nazi euthanasia program[4,5,8].

In the 1920s, Creutzfeldt (figure 1) and Alfons Jacob (figure 2) independently described a syndrome characterized by progressive dementia, ataxia, tremors, and death.

Creutzfeldt, in 1920[3], reported a detailed case of a 23-year-old woman with an unusual combination of neurological signs and pathological findings under the title "Über eine eigenartige herdförmige Erkrankung des Zentralnervensystems" ("About a peculiar focal disease of the central nervous system"). In that report, Creutzfeldt distinguished the condition from multiple sclerosis and termed it "pseudosclerosis". He concluded with caution that it was a unique disease process that occurred in a young woman with the following characteristics: 1. Unknown cause (perhaps family predisposition), 2. Episodic course with remissions, 3. Cortical symptoms in the domain of motor and sensory centres (spasms and hyperalgesia), 4. Psychic symptoms of amental nature [dementia] with a predominance of psychomotor phenomena, 5. Progressive course, 6. Non-inflammatory focal destruction of the cerebral cortex with neuronophagy and reparative glial proliferation (sometimes with vascular proliferation), 7. Diffuse non-inflammatory cell disease with cell loss in the domain of almost all grey matter.

In 1921, Jakob published three articles, "On peculiar illnesses of the central nervous system with remarkable anatomical findings"[6], and also a separate article (1923), where he described five cases of patients who died of rapidly progressive dementia (between a few weeks and a year after starting more severe symptoms)[6]. Jakob designated that disease as a 'Spastic pseudosclerosis encephalopathy with disseminated foci of degeneration' because he believed that it resembled multiple sclerosis and amyotrophic lateral sclerosis[4]. However, retrospective postmortem examination by Masters, Gajdusek, and Richardson, apud Pearce[8], revealed the cardinal vacuolation of the cerebral cortex and cerebellum in only two of Jakob's five patients. Consequently, only these cases are now considered to be under the label of CJD. Besides, Creutzfeldt's case is not deemed to be a CJD case, as clinical and pathological findings do not represent the transmissible spongiform encephalopathy group[6].

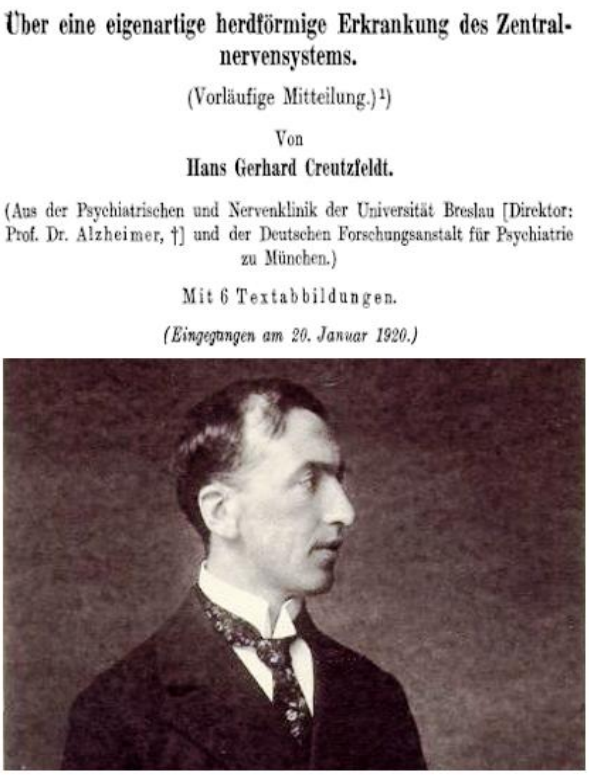
Surprisingly, Jakob gave credit to Creutzfeldt for describing the syndrome before him, as he concluded that Creutzfeldt's case refers to a "nosologically very closely connected if not identical affection", apud Katscher[6].

Furthermore, Walther Spielmeyer reinforced Creutzfeldt's pioneering when, for the first time, used the term "Creutzfeldt-Jakob disease", in 1922. In fact, Duckett & Stern[4] believe that it is not possible to justify the use of the term 'disease' as Spielmeyer did. That would happen because of the neuropathological school rivalries between Spielmeyer and Jakob. Spielmeyer's gesture in creating this 'disease' was unfortunate because of the confusion it ultimately caused. Duckett & Stern[4] declare that neither Creutzfeldt nor Jakob used the eponyms Creutzfeldt Jakob disease or Jakob-Creutzfeldt disease. Both concluded that they had described a neuropathological syndrome associated with features of many disorders, rather than a disease itself, which still appears vindicated[4].

In 1929, Heidenhain, apud Pearce[8], reported three patients, two of them with cortical blindness and significant spongy changes that became known as the Heidenhain variant of CJD.

Over time, it was recognized that the archetypal human prion disease is the sCJD, as first described by Jakob.

Many unfoldings happened in studying this intriguing disease, and today it is known as one of the prion diseases. Figure 3 presents some landmarks of the acquisitions on spongiform encephalopathies, including mainly CJD matters.



Über eine eigenartige herdförmige Erkrankung des Zentralnervensystems.

(Vorläufige Mitteilung.)[1])

Von

Hans Gerhard Creutzfeldt.

(Aus der Psychiatrischen und Nervenklinik der Universität Breslau [Direktor: Prof. Dr. Alzheimer, †] und der Deutschen Forschungsanstalt für Psychiatrie zu München.)

Mit 6 Textabbildungen.

(Eingegangen am 20. Januar 1920.)

Figure 1. Hans Gerhard Creutzfeldt (June 2, 1885 Harburg upon Elbe, Hamburg -December 30, 1964, Munich, aged 79) and his 1920 paper[3,4,8].

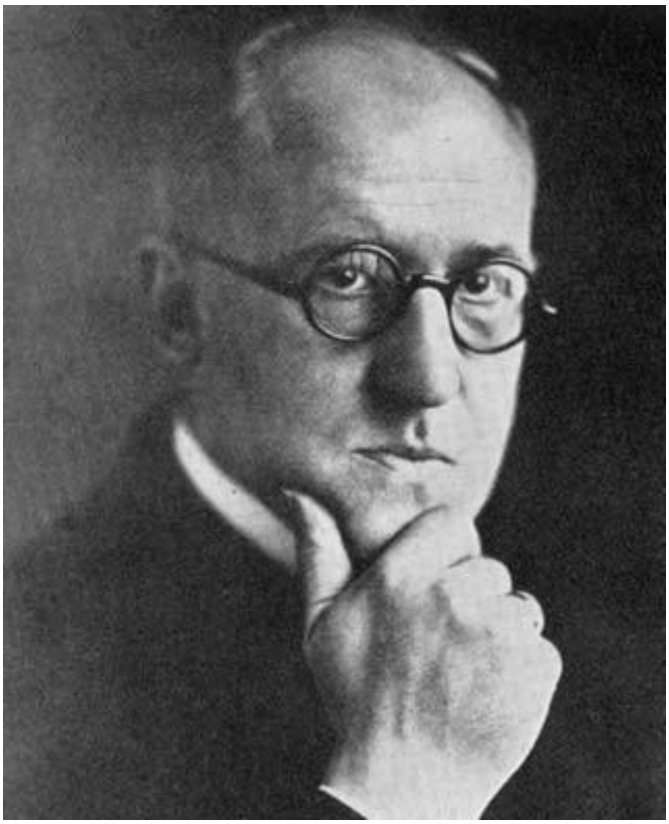


Figure 2. Alfons Maria Jakob (July 2 1884, Aschaffenburg/Bavaria-October 17, 1931, Hamburg, aged 47). He had worked at the Friedrichsberg State Hospital in Hamburg, 1911, in the pathological-anatomical laboratory led by Theodor Kaes, and succeeded him. He was trained by Alzheimer in Munich in 1911–1912[4,8].

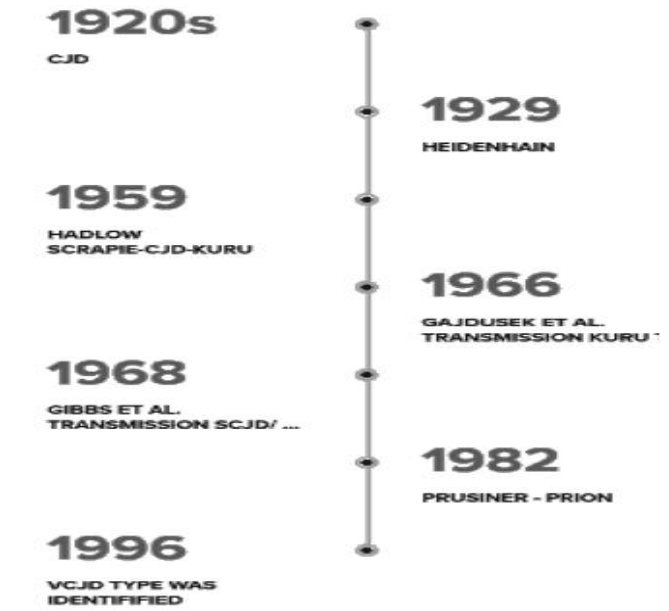


Figure 3. Marcos das descobertas de doenças por príons e a CJD incorporada: clinical and pathological characteristics, interspecies transmission and the unusual causal agents [9,10].

CREUTZFELDT–JAKOB DISEASE NOWADAYS

Prion diseases or transmissible spongiform encephalopathies encompass human and animal illnesses. Concerning the human ones, three groups are acknowledged:
1-Sporadic (Sporadic Creutzfeldt-Jakob disease -sCJD, sporadic fatal insomnia, and variably protease-sensitive prionopathy);
2-Genetic (Genetic Creutzfeldt-Jakob disease -gCJD, fatal familial insomnia-FFI, and Gerstmann-Sträussler-Scheinker syndrome-GSS);
3-Acquired (Kuru, iatrogenic CJD-iCJD, variant CJD-vCJD). Regarding these last ones: Kuru (in Papua New Guinea, from the ingestion of infected brain tissue during cannibalistic mortuary rites) or caused by previous medical or surgical treatments - iCJD, or a vCJD, as a zoonosis causally linked to the bovine spongiform encephalopathy [9].

This last type, vCJD, occurs in patients with a median duration of illness between 13 to 14 months, and the median age of death is 28 years. vCJD was identified in 1996 as a novel human prion disease, and its appearance in the United Kingdom led to the hypothesis that this disease was linked to the so-called bovine spongiform encephalopathy [9].

The archetypal human prionic disease is sCJD. However, various sCJD distinct clinical patterns phenotypes vary based on classification. Individuals who display features of sCJD variant may also have unique genetic or other disease-altering variables. Appleby et al.[1] give support to the existence of 5 sCJD variants in addition to the 3 previously reported variants: classic CJD (n=11); Heidenhain (n=15); and Oppenheimer-Brownell (n=8); along with 2 neuropsychiatric variants, cognitive (n=28) and affective (n=13). Depending on genotypes and prion proteins, these phenotypes may be divided into six subtypes largely correlated with variables as age at onset of symptoms [9].

CJD is now recognized as a group of diseases that are most often characterized by rapidly progressive dementia with myoclonus, ataxia, and often seizures. sCJD affects middle-aged individuals of both sexes. The time from symptom onset until death is variable, ranging from weeks to years. sCJD, which accounts for the majority of cases, results in the most rapid decline. However, the disease course of sCJD variants as Heidenhain and Oppenheimer-Brownell may arise later than the classical sCJD. The former is characterized by visual symptoms at onset, including diplopia, visual field defects, hallucinations, and/or cortical blindness. The Oppenheimer-Brownell variant presents with ataxia at the onset. They have median survival times that maybe the double of that of a typical sCJD.

In general, much has already been discovered about the origins of sCJD. It was connected to the spontaneous misfolding of the normal prion protein (PrP^{C}) into a disease-associated isoform (PrP^{Sc}), supposedly due to a random mutation.This abnormal misfolding leads to brain damage and the characteristic symptoms of the disease. Besides, mutations in the normal prion protein encoded by the PRioN Protein (PRNP) gene are linked to genetically inherited prion diseases, including genetically associated CJD, GSS and FFI. PrP^{C} is encoded by a single gene, which is located in chromosome 20 and is known as the PRNP gene [7].

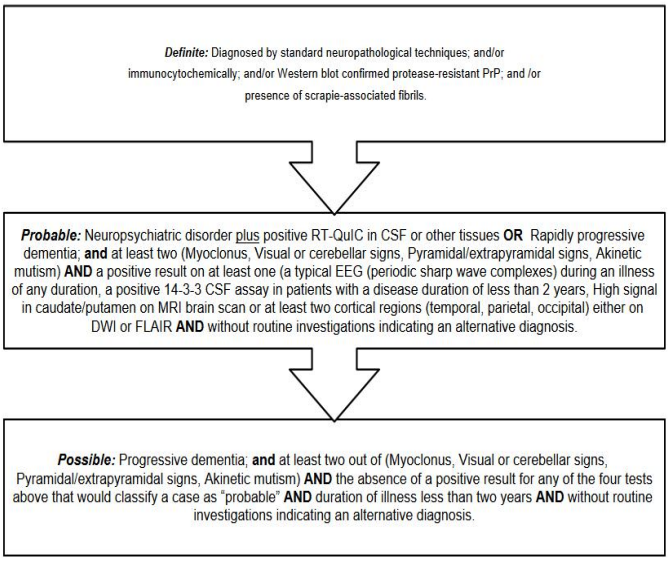


Figure 4. CJ diseases hallmarks and diagnostic criteria: sporadic CJD[2].

In short, the designation CJD would assume that the aetiology or its unmistakable anatomopathological findings would be known. This definition would represent the highest level of conceptual understanding of the disease. On the contrary, a syndrome, as in fact the precursor authors pointed out, would have been better applied to the series of symptoms and signs that occurred together or varied over time. Consequently, at the time of Creutzfeldt and Jakob, when prionic diseases were not yet known, let alone their typical anatomopathological patterns, the term, syndrome, would fit better in what is now known as sCJD[4]. These pioneers, however, contributed to the paving of this rich route that configured the family of spongiform encephalopathies. Congratulations to them on the 100th anniversary of their first publication on their "pseudosclerosis".

FUNDING STATEMENT:
The author did not receive funding for this work.

DECLARATION OF AUTHOR COMPETING INTERESTS:
The author declares no competing interests.

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