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CREUTZFELDT-JAKOB DISEASE

A SURVEY OF 14 PATIENTS

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ABSTRACT - Creutzfeldt-Jakob disease (CJD) is a transmissible disease of the nervous system causatively related to the presence of an abnormal prion protein, with dementia, myoclonic jerks, and periodic EEG activity. Fourteen patients (7 females and 7 males) ranging from 26 to 76 years of age (median 59 years) were evaluated between 1974 and 1995 at the Neurologic Clinic of São Paulo University School of Medicine. The average duration of the disease was 12 months (3.5 - 34 months). Early clinical findings were: behaviour changes in 7 patients, dementia in 4, visual disturbances in 4, vertigo in 2, tremor in 9, and dystonia in one. Advanced symptoms were dementia and myoclonus in all patients. Pyramidal tract dysfunction was found in 6, cerebellar ataxia in 2, seizures in 3, nystagmus and vertigo in 4, and peripheral nervous system involvement in 2. Atypical clinical forms were found in 5 patients. Periodic EEG activity was found in 10 patients. Cerebrospinal fluid evaluation showed pleocytosis in 1 patient, higher protein content in 2, and higher gamma globulin level in 2. In 10 patients anatomopathological evidence in the central nervous system confirmed the clinical diagnosis by presenting with status spongiosus. All except one patient presented with the sporadic form of the disease.

KEY WORDS: prion disease, Creutzfeldt-Jakob disease, spongiform encephalopathy.

Doença de Creutzfeldt-Jakob: relato de 14 pacientes

RESUMO - As encefalopatias espongiformes humanas ou doenças priônicas são um grupo de doenças rapidamente progressivas caracterizadas por déficit cognitivo, ataxia, mioclonia e manifestações visuais, piramidais e extrapiramidais. A doença de Creutzfeldt-Jakob (DCT) pode apresentar forma iatrogênica, genética e esporádica. Os autores apresentam 14 pacientes com DCJ forma esporádica e um com forma familial, acompanhados na Disciplina de Neurologia Clínica da FMUSP, no período de 1974 a 1995. Sete eram do sexo feminino e 7 do sexo masculino, com idade variando de 26 a 76 anos (média de 59 anos). As manifestações neurológicas iniciais foram distúrbio do comportamento em 7, demência em 4, deficiência visual em 4, vertigens em 2, tremor em 9 e distonia em um paciente. Posteriormente, demência e mioclonias ocorreram em todos os pacientes. Foram encontrados: disfunção do trato piramidal em 6, vertigens em 4, convulsões em 3, ataxia cerebelar em 2, distúrbio do sistema nervoso periférico em 2. A forma atípica da doença ocorreu em 5 pacientes. Atividade periódica ao eletroencefalograma ocorreu em 10 pacientes. O líquido cefalorraquidiano mostrou pleocitose em 1, hiperproteinorraquia em 2 e hipergamaglobulinorraquia em 2. O estudo anátomo-patológico do sistema nervoso central, feito em 10, revelou alterações vacuolares do neurópilo em todos os pacientes.

PALAVRAS-CHAVE: prions, doença de Creutzfeldt-Jakob, encefalopatia espongiforme.

The human transmissible spongiform encephalopathies (TSEs), or prion diseases, are a group of rapidly progressive and lethal disorders with spongiform (vacuolar) degeneration and variable

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amyloid plaque formation of the central nervous system (CNS), caused by prion. The TSEs are Kuru, an infectious disease; Creutzfeldt-Jakob disease (CJD) which may take an infectious, genetic, and sporadic form; and Gerstmann-Straussller-Scheinker disease (GSS) and fatal familial insomnia (FFI), rare familial disorders. With exception of FFI, all of these disorders have been experimentally transmitted to nonhuman primates and laboratory rodents[13].

CJD was first reported in 1920, and since then has been clinically characterized by dementia associated with the motor deficit, ataxia, spasticity or extrapyramidal dysfunction, especially myoclonus[20]. In 1960, the electroencephalography (EEG) disclosed periodic paroxysmal activity as well as anatomopathological changes with neuronal loss, spongiform degeneration and astrocytosis[16]. Major progress to characterize the disease were made in 1968, when it became possible to transmit the disease to experimental animals by inoculation of brain material from infected patients and when spongiform encephalopathies in other animals such as cattle, sheep and mink were confirmed[21]. Scrapie in sheep and bovine spongiform encephalopathy (*mad cow disease*) are close analogs of human TSE[13]. As such, the association with a transmissible agent having no similarity with known pathogens was proven, permitting Prusiner, in 1982, to introduce the term prion, to designate the infectious particles deprived of nucleic acid found in the central nervous system of afflicted patients[18,26].

CJD seems to have been iatrogenically transmitted by corneal graft[11,13], intracerebral electrodes, failure to sterilize surgical instruments[12,13] and implantation of dura mater homografts[13]. The incubation period of accidental transmission does not seem to exceed 18 months, but transmission from an infected hypodermic needle or dentist's drill might cause overt diseases years or decades later. The most common source of iatrogenic CJD has been contamined human growth hormone derived from cadaveric tissues[13]. A search for possible unrecognized cases revealed instances in England and France in which several patients developed CJD within two years of undergone neurosurgical procedures in the same operating rooms previously used for operations on patients with CJD[13]. CJD is a geographically unrestricted disease; the incidence is of 0.5-2/10^6 inhabitants per year[2,16].

The objectives of this study are to describe the clinical, electroencephalographic, and anatomopathological evaluation of 14 patients with CJD, stressing the atypical expression of the disease.

PATIENTS AND METHODS

Fourteen patients were evaluated in the study, as they fulfilled the previously established criteria for CJD, from 1974 to 1995, at the Neurologic Clinic of the São Paulo University School of Medicine. Patients with the former frontal pyramidal form[1], currently known as lateral amyotrophic sclerosis with dementia[17,23], were excluded.

Clinical examination and epidemiological data stressed age of onset, initial symptoms, neurological signs and clinical progression, duration of the disease, personal history related to surgery or blood transfusion, and familial history. Nationality and origin of the patients were emphasized.

All patients were submitted to EEG. Cerebrospinal fluid (CSF) was obtained in 11, 2 underwent brain scintiscan with technetium (Tc), 2 were submitted to pneumoencephalography (PEG), 7 had a brain computerized tomography (CT Scan) study, and 3 had brain magnetic resonance image (MRI). Electroneuromyography (ENMG) was undertaken in 3 patients and an anatomopathological study of the brain in 9. Of the 4 cases with no anatomopathological study, in 2 the autopsy was not done because of family refusal and the remaining 2 are still awaiting for a conclusion.

RESULTS

Data of the clinical, neurological, and laboratorial findings of the 14 patients are found on Tables 1, 2 and 3.

Seven of the patients were female and 7 male. The age of onset of the disease ranged from 26 to 76 years of age (median of 59 years). Average duration of the symptoms until death was of 12 months (3.5 to 34 months).

Table 1. Identification, progression and history

Patient Record	Age (years)	Race/ Sex	Age at Onset (years)	Duration and progression of illness (months)	History
1. EGRP. 1.043.216	52	W M	52	6	-
2. SG 000.111	66	W F	64	31	-
3. LRS 000.163	50	W M	50	4.5	-
4. FAR 1.155.193	62	W M	62	12	-
5. FLA 2.010.472-E	61	W F	61	6	-
6. NS 00.506	52	Pale M	50	25	-
7. BBF 2.246.933-K	65	W M	65	4	-
8. SSF 2.852.522-C	71	W M	71	6	-
9. VAA	73	W F	73	3.5	Surgery at 73 years old
10. MRARP 2.604.535-I	26	W F	24	34	Cesarian at 22 years old
11. EM	56	W	56	3.5	Surgery at 56 years old
12. JPM 2.046.436-I	66	W F	66	8	Surgery at 48 years old
13. GBSA 3.023.484-D	76	W F	76	6	-
14. JFB	43	W	43	5	Familial

W, white; F, female; M, male; -, absent.

The most frequent opening symptoms were behaviour changes in 7 patients characterized by irritability, depression, anxiety, decline of initiative and interest, emotional lability, insomnia, and periods of mental confusion with visual hallucinations. Blurred vision, decline of visual acuity, multiple scotomas, or quadrantonopia were the observed visual symptoms and the second most frequent initial symptoms, found in 3 patients. Two patients exhibited upon admission more than one symptom: behaviour changes and vertigo in one, dystonia and visual disorders in another.

The SG patient presented with an abrupt onset of symptoms: visual impairment and that of extrinsic ocular motility, leading to the initial suspicion of a vascular disease. Patients VAA and EM exhibited symptoms in the immediate postoperative. Patient MRARD presented with clinical symptoms during the 3rd month of pregnancy. During the course of the disease, all patients had dementia and myoclonus. The other signs of progression of the disease are on Table 2.

None of the patients had metabolic disorders which might justify symptoms such as hyperparathyroidism [4]. In 4 patients with no anatomopathological study of the encephalon, the triad dementia, myoclonus, and periodical activity at EEG, led to the diagnosis.

Table 2. Frequency of neurological changes at onset and progression

Clinical findings	Initial		Progression	
	n	%	n	%
Behaviour findings	7	50	10	71
Dementia	3	28.5	14	100
Myoclonus	-	-	14	100
Cerebellar signals	1	7	2	14.3
Pyramidal syndrome	-	-	10	71
pyramidal deficit			8	57
pyramidal liberation			8	57
Extrapyramidal syndrome	1	7.1	6	43
rigid akinetic	-	-	5	35.7
tremor	-	-	2	14.3
dystonia	1	7.6	2	14.3
Motor peripheral syndrome	-	-	2	14.3
muscle atrophy	1	7.1		
Total	3	23	7	50
visual changes	4	28.5	4	28.5
ocular motility changes	-	-	1	7.1
nystagmus	-	-	3	21.4
Vertigo	2	14.3	3	21.4
Seizures	-	-	3	21.4

DISCUSSION

In the current study, we observed that the incidence of CJD was similar in both sexes, with a peak at the 6th of life, in accordance with observations of other authors[16]. Only one patient had previous familial history; although, in large series this data may range from 6 to 45%[15,16]. Research of transmissible agents disclosed that none of the patients had a history of blood transfusion and only 4 had been submitted to surgery; however, with no access to the central nervous system (CNS). Masters et al.[15] report a median incubation time of 3 years for iatrogenic cases of CJD, but none of our patients fits into this category. One patient began to present symptoms during pregnancy and 2 at the immediate postoperative, in a sudden manner. We believe that although there is no causative relation, pregnancy and surgery might have contributed to worsening the disease.

In this casuistics the average course of 12 months remains in the upper limit of the referred average course of 6 to 12 months[20]. However, there are reports on longer courses of 4 to 6 years[24]. The longest course was that of patients in which behaviour changes defined the onset of symptoms[2,5,9], with an average surgical period of 25 months. The remaining patients of this series, separately evaluated, survived for 5 months. Expression was atypical in 5 patients, with isolated visual, extrinsic ocular motility, cerebellar or dystonic features which delayed diagnosis.

Table 3. Auxiliary tests

Case	Electroencefalography	Cerebrospinal fluid	Image	Electroneuro myography	Anatomo pathology
1.	periodic activity	normal	99Tc increase left	fasciculations	SS
2.	slow and desorganized cerebral waves	protein 41 mg%	Peg with cerebral atrophy	-	SS
3.	periodic activity	normal	-	fasciculations	SS
4.	frontal desorganization of waves	normal	normal Peg & 99Tc	fasciculations	SS
5.	periodic activity	normal	-	-	SS
6.	slow 7 desorganized right temporal spicuale	-	-	-	SS
7.	periodic activity	-	CT ventricular enlargement	-	SS
8.	periodic activity	41 cells/mm^3; 21.1% gamma globulin	CT cerebellar atrophy; MRI: multifocal disease of white matter	-	SS
9.	periodic activity	normal	CT brain atrophy	-	SS
10.	periodic activity	gamma globulin 17%	CT & MRI brain atrophy	-	WAR
11.	periodic activity	protein 61 mg%	CT normal brain	-	-
12.	periodic acrivity	normal	CT & brain atrophy	-	WAR
13.	periodic activity	normal	CT & MRI normal brain	-	-
14.	slow and desorganized waves	normal	hypodense lesions of frontal and parietal; 2 months later occurred cerebral atrophy	-	SS

99Tc, 99 technetium; Peg, pneumoencephalography; CT, computerized tomography; MRI, magnetic resonance image; SS, status spongiosus; -, not done; WAR, without anatomopathological results.

In 10 patients (71%) onset of the disease started with mental disorders: dementia or behaviour disturbances, a quite close rate to the 64% reported by Brown et al[6] in an analysis of 230 patients with anatomopathological study. However, while in the Brown series visual and cerebellar disorders were the starting symptoms, respectively in 17 and 34%, in this series such a ratio is inverted, with the visual form corresponding to 23% and the cerebellar one only to 7.6%. Other series show a higher initial frequency of cerebellar signs, ranging between 11 and 41%[14,21,28,30].

As for progression, patients showed the expected frequency of dementia and myoclonus, clinical markers of the CJD, as well as of the remaining signs, again with exception made to the cerebellar syndrome, responsible for only 15.3% against 42 and 61% in other series[6,14,25,28,30]. Furthermore, pyramidal syndromes had a much higher incidence, 75% against 43% of the formerly

described. As stressed by Yasuda[31], the large number of pyramidal and extrapyramidal signs may hinder disclosure of cerebellar signals in these patients.

Even excluding patients with the previously described frontal pyramidal form [1] currently characterized as amyotrophic lateral sclerosis with dementia[17,23], from 12 to 38% of patients presented with clinical impairment of the peripheral motor neuron and/or electromyographical or anatomopathological disturbances suggestive of anterior horn[9,27] as observed in 3 of our patients.

Sixty-five percent of our patients presented with periodical paroxysmal discharges at EEG, more frequent during the course of the disease and which might not be evident during the prodromal and terminal stages[7,21]. Changes of CSF, such as slight protein content increase, pleocytosis and gamma globulin elevations are reported for 20% of patients[28,31], a lesser number than the 40% found here.

Brain CT scan , as well as the other reviewed imaging assays, shows cerebral atrophy and MRI might disclose increase of signals in the thalamus and basal ganglia[9].

Pathology of CJD is characterized by spongiform changes with small vacuoles in the neuropil, gliosis, neuronal loss, absence of inflammatory activity, and of major white matter impairment. Electron microscopy aids to differentiate the described spongiform changes from the status spongiosus, considered less specific for the diagnosis of CJD[21]. All patients submitted to autopsy presented changes compatible with the diagnosis, and in Patient 1 electron microscopy confirmed the diagnosis. In the patients submitted to autopsy no other processes that could be held responsible for death were found. For instance, patients with bronchopneumonia presented with a mild case with no signs of sepsis. In such cases death could result from impairment of multiple systems of the CNS, essentially by lesion of autonomic nervous system, leading to a cardio-pulmonar dysfunction.

There is no known effective therapy for CJD and diagnosis is confirmed by reproducing the disease in an animal inoculated with brain tissue extracted from a suspected patient. Currently the etiology of CJD relates to the prion, small proteinaceous infectious particles resistant to many procedures that inactive nucleic acids, which are found in purified brain fractions of animals affected by spongiform encephalopaties such as scrapie of sheep[20,21]. However, the scrapie prion, -PrPsc, has a normal cellular homologue-PrPc with different biological properties[18,26]. It is believed that PrPsc derives from normal protein, with which an inoculated exogenous abnormal prion agent would interact. However, other theories under advocate a somatic mutation of the PrP gene, spontaneous post-translation changes of: PrPc into PrPsc, a genetically into PrPsc, or a genetically determined susceptibility to environmental factor of familial, sporadic iatrogenic CJD, besides studies of molecular genetics, points out that probably this illness is a syndrome with multiple molecular, clinical and neuropathological features[5,7,22]. Prions, once dismissed as an impossibility, have now gained wide recognition as extraordinary agents that cause a number of infectious, genetic, and spontaneous disorders[29].

In any case, once present in the nervous system, the abnormal prion protein spreads to the healthy neurons in a chain reaction, leading to spongiform changes and, finally to neuron loss with reactional astrocytosis[10,19].

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