Prion diseases
Doenças priônicas
Abelardo Q-C Araújo

ABSTRACT
Prion diseases are neurodegenerative illnesses due to the accumulation of small infectious pathogens containing protein but apparently lacking nucleic acid, which have long incubation periods and progress inexorably once clinical symptoms appear. Prions are uniquely resistant to a number of normal decontaminating procedures. The prionopathies [Kuru, Creutzfeldt-Jakob disease (CJD) and its variants, Gerstmann-Sträussler-Scheinker (GSS) syndrome and fatal familial insomnia (FFI)] result from accumulation of abnormal isoforms of the prion protein in the brains of normal animals on both neuronal and non-neuronal cells. The accumulation of this protein or fragments of it in neurons leads to apoptosis and cell death. There is a strong link between mutations in the gene encoding the normal prion protein in humans (PRNP) - located on the short arm of chromosome 20 – and forms of prion disease with a familial predisposition (familial CJD, GSS, FFI). Clinically a prionopathy should be suspected in any case of a fast progressing dementia with ataxia, myoclonus, or in individuals with pathological insomnia associated with dysautonomia. Magnetic resonance imaging, identification of the 14-3-3 protein in the cerebrospinal fluid, tonsil biopsy and genetic studies have been used for in vivo diagnosis circumventing the need of brain biopsy. Histopathology, however, remains the only conclusive method to reach a confident diagnosis. Unfortunately, despite numerous treatment efforts, prionopathies remain short-lasting and fatal diseases.

Keywords: prion, Creutzfeldt-Jakob disease, dementia, slow viruses.

RESUMO
Doenças priônicas são enfermidades neurodegenerativas devido ao acúmulo de pequenos agentes infecciosos compostos unicamente por proteína (prions), com longos períodos de incubação e de progressão inexorável para o óbito. Essas agentes são excepcionalmente resistentes aos processos habituais de descontaminação para gérms e vírus. As prionopatias [Kuru, doença de Creutzfeldt-Jakob (CJD) e suas variantes, Síndrome de Gerstmann-Sträussler-Scheinker (GSS) e insônia familiar fatal (FFI)] resultam do acúmulo de isoformas anormais da proteína priônica no cérebro. Este acúmulo leva, em última análise, à apoptose e morte celular. Existe uma forte associação entre mutações no gene que codifica a proteína priônica normal em humanos (PRNP) - localizado no braço curto do cromossoma 20 – e formas genéticas destas doenças (CJD familiar, GSS, FFI). Clinicamente devemos suspeitar de uma prionopatia em qualquer caso de demência de rápida progressão, particularmente quando associadas a ataxia, mioclonias, ou em indivíduos com insônia patológica combinada com disautonomia. Métodos diagnósticos como ressonância magnética, pesquisa da proteína 14-3-3 no líquido cefalorraquiano, biópsia de amígdalas e estudos genéticos têm sido utilizados para diagnóstico in vivo, evitando-se assim a necessidade de biópsia cerebral. A despeito disso, a histopatologia continua a ser o único método conclusivo para se chegar a um diagnóstico definitivo. Infelizmente, apesar dos inúmeros esforços de tratamento, as prionopatias permanecem doenças de curta duração e fatais.

Palavras-Chave: prion, doença de Creutzfeldt-Jakob, demência, virose lenta.

When Stanley Prusiner coined the term “prion” in 1982, which he defined as a small infectious pathogen containing protein but apparently lacking nucleic acid, the scientific world watched amazed a revolution in the fields of biology and medicine\(^1\). Finally unveiling the cause of a group of mysterious diseases known by veterinarians since 1730, when the first cases of scrapie appear in Central Europe and England, Prusiner deservedly won the 1997 Nobel Prize for his achievement. Before him Carleton Gajdusek had won the same prize in 1976 for his discoveries in this field.

In fact, like in other subjects, Prusiner was picking up on an idea originally proposed in the 1960s, when Tikvah Alper and J. S. Griffith from London, suggested that an infectious agent that lacked nucleic acid could cause disease. Such an idea seemed to threaten the very foundations of molecular biology, which held that nucleic acids were the only way to transmit information from one generation to the next\(^2\).

Biology
Prions are small infectious pathogens containing protein but apparently lacking nucleic acid\(^3\). The “protein only” hypothesis proposes that the pathological prion protein (PrP\(^\text{Sc}\)) is a conformational isoform of a normal host protein (PrP\(^\text{C}\)), which is found predominantly on the outer surface of...
neurons, attached by a glycosylphosphatidyl-inositol (GPI) anchor. The abnormal conformer (PrPSc), when introduced into the organism – by external routes or by mutations – is thought to cause the conversion of the normal PrPc into a likeness of itself (PrPSc) (akin to the dual-personality characters described in the novel by Robert Louis Stevenson, The Strange Case of Dr Jekyll and Mr Hyde). Because the amino acid sequences of PrPc and PrPSc are often identical, the cause of their functional differences is attributed to their variance in structure, and not to any chemical dissimilarity. Whereas PrPc consists primarily of alpha helices and very few beta sheets, PrPSc, though having the same primary structure, consists in large part of beta sheets. As yet, it is still unclear exactly what causes the flip from PrPc to PrPSc.

After the transformation of one prion, the process continues at an exponential rate, eventually infecting the entire brain of the host and causing irreparable damage. Once PrPc adopts the beta-sheet structure of PrPSc, it becomes detached from the cell membrane and is absorbed by vesicles within the cell. In particular, it begins to accumulate in the cell’s lysosomes. The accumulation of PrPSc in the lysosomes causes them to swell and eventually burst, thereby releasing the damaging proteolytic enzymes and PrPSc into the cell. In contrast to PrPc, PrPSc accumulates within cells and does not normally appear on the cell surface. PrPSc appears to be neurotoxic, its accumulation leading to apoptosis and cell death.

In addition to the mode of infection outlined above, that is, through sporadic conformational transformation, infective prions can also be transmitted from one individual to another during medical procedures such as tissue transplantation and injection of growth hormones, as well as contaminated surgical instruments. Yet a third mode of infection is through the inheritance of mutated genes that increase the likelihood of conformational change in the prions for which they are responsible.

One characteristic feature of prions is their resistance to a number of normal decontaminating procedures. They are resistant to processes affecting nucleic acids, such as hydrolysis or shearing. Thus, suspected prion-contaminated medical instruments require specific procedures.

Prions can be transmitted between members of different species. This phenomenon is known as the violation of the species barrier. The determining factor seems to be the degree of similarity between the two species of prions. This fact became cause of a great deal of anxiety caused by the outbreak of epidemic bovine spongiform encephalopathy (BSE, or mad cow disease). If one compares the overall evolutionary relationship of humans and cows, the general features of prions, there seems to be little cause for worry; however, it is possible that bovine prions might be similar enough to human prions to be able to cross the species barrier and infect human hosts with what was originally a bovine disease.

Genetics

The gene encoding the normal protein in humans (PRNP) is located on the short arm of chromosome 20. A strong link was established between mutations in this gene and forms of prion disease with a familial predisposition (familial Creutzfeldt-Jakob disease (fCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomina (FFI)). A single mutation can produce different clinical phenotypes in different individuals or families. More than 50 different mutations have been identified so far. This is why some experts have advocated classifying prion diseases based upon the responsible mutation rather than the traditional classifications.

The codon 129 of the PRNP gene is polymorphic; normal individuals have either valine or methionine at that site. Neither V129 nor M129 appears to be pathogenic by itself. Patients with the D178N mutation who are homozygous for valine at codon 129 appear to develop fCJD, while those who are homozygous for methionine tend to have FFI.

All GSS kindreds investigated to date have PRNP gene mutations, being the P102L mutation the most common. In fCJD, a missense mutation involving the substitution of glutamine for glutamine in codon 200 is the most common gene mutation worldwide. The D178N mutation has been the predominant mutation found in nearly all families with FFI. This mutation also occurs in fCJD. It appears that patients with this mutation who are homozygous for methionine at codon 129 develop an FFI-like clinical syndrome whereas those homozygous for valine develop fCJD.

Clinical aspects

Five established human prion diseases are currently recognized: Kuru, Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD also known as new variant CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). However, a new prion disease named “proteinase-sensitive prionopathy” was described in 2008. Patients presented at a mean of 62 years with a dementia with prominent neuropsychiatric manifestations and progressive motor decline (ataxia and/or parkinsonism). Death followed symptoms onset within a mean of 20 months. A family history of dementia was present in many patients, suggesting a possible genetic origin. CSF 14-3-3 was negative in all individuals, magnetic resonance imaging (MRI) demonstrated diffuse atrophy without restricted diffusion, and electroencephalogram (EEG) were normal or showed only diffuse slowing. Neuropathologic examination revealed spongiform degeneration in the cerebral cortex, basal ganglia, and thalamus with relative sparing of the brainstem and cerebellum. There was a similar anatomic distribution of PrP immunostaining but, intriguingly and differently from all other prion diseases, its immunoreactivity was virtually abolished by protein digestion. All of these cases had the 129VV
genotype. Since its original description more cases have been reported\textsuperscript{12}.

Table 1 summarizes the main aspects and differences between the classical prionopathies.

1. Kuru

Kuru (which means shivering in the Faroe language), which was endemic in Papua New Guinea among the Fore tribes, used to be transmitted from person to person by ritual cannibalism. The cessation of these practices in the 1950s ended incident cases of kuru; however, 11 new cases have been identified between July 1996 and June 2004, with a likely incubation period of more than 50 years in some\textsuperscript{13}.

No mutations in the PRNP gene have been reported in kuru, however, like in CJD and in its variants, homozygosity at the polymorphic codon 129 of the PRNP gene has been detected more frequently\textsuperscript{14}.

2. Gerstmann-Sträussler-Scheinker syndrome (GSS)

GSS is inherited in an autosomal dominant pattern with virtual complete penetrance. Its diagnosis cannot be made from the usual laboratory or imaging studies. Demonstration

<table>
<thead>
<tr>
<th></th>
<th>Kuru</th>
<th>GSS</th>
<th>FFI</th>
<th>sCJD</th>
<th>vCJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Extinct</td>
<td>1-10/100 million inhabitants/year</td>
<td>Sporadic, in families</td>
<td>1/1 million inhabitants/year</td>
<td>Sporadic, &lt;230 cases described so far</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Variable*</td>
<td>43-48</td>
<td>56</td>
<td>57-62</td>
<td>29 (11-74)</td>
</tr>
<tr>
<td>Dementia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ataxia</td>
<td>+++; tremors</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>+ (choreoathetosis, fasciculations)</td>
<td>+ (dysesthesia, hyporeflexia, proximal weakness)</td>
<td>+++ (progressive insomnia, dysautonomia, abnormal circadian rhythm of hormone secretion)</td>
<td>+ (mainly in younger cases)</td>
<td>+++ (early and prominent**)</td>
</tr>
<tr>
<td>Other neurological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathology</td>
<td>PrPSC-reactive plaques (Kuru plaques) mainly in the cerebellum, neuronal loss, hypertrophy of astrocytes</td>
<td>Kuru-like plaques in highest density in the cerebellum</td>
<td>Spongiform degeneration rare, neuronal loss and gliosis maximal within the thalamus, cerebellum and olivary nuclei</td>
<td>Spongiform changes, neuronal loss (cortical layers III-V), no inflammation, accumulation of PrP\textsubscript{Sc}</td>
<td>Florid or cluster amyloid plaques (PrP\textsubscript{Sc} +)****, throughout the cerebrum, cerebellum and lesser in the basal ganglia/thalamus.</td>
</tr>
<tr>
<td>Genetics</td>
<td>No mutations, homozygotes at codon 129</td>
<td>Autosomal dominant, mainly P102L PRNP gene mutation</td>
<td>Mainly D178N PRNP gene mutation</td>
<td>No mutations but homozygosity for val or met at codon 129 confers susceptibility</td>
<td>No mutations but virtually all patients are homozygous for met at codon 129</td>
</tr>
<tr>
<td>EEG</td>
<td>Abnormal slowing, unspecific</td>
<td>Abnormal slowing, unspecific</td>
<td>Normal</td>
<td>PSWC</td>
<td>Abnormal slowing; PSWCs generally not seen except rarely in the later stages of disease</td>
</tr>
<tr>
<td>CSF</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>14-3-3 protein ++</td>
<td>Normal. 14-3-3 in less than half of patients</td>
</tr>
<tr>
<td>MRI</td>
<td>Unknown</td>
<td>Areas of decreased T2 signal in the striatum and midbrain</td>
<td>Normal</td>
<td>Increased T2/FLAIR signal intensity in the putamen and head of the caudate</td>
<td>Hyperintensity in the pulvinar (pulvinar sign) or in both pulvinar and dorsomedial thalamus (hockey stick sign), which may disappear on follow-ups</td>
</tr>
<tr>
<td>Time to death (months)</td>
<td>9-24****</td>
<td>5</td>
<td>13</td>
<td>4-5</td>
<td>14</td>
</tr>
</tbody>
</table>

Notes: (-) uncommon, (+) present but usually late, (++) usual, (+++) very frequent; Sporadic Creutzfeldt-Jakob disease (sCJD), variant Creutzfeldt-Jakob disease (vCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI); * usually in children and females in the beginning of the epidemics, age at onset increased since the cannibalism practice was banned; (PSWC) periodic synchronous bi- or triphasic sharp wave complexes; ** depression, apathy, anxiety, irritability, social withdrawal, agitation, and insomnia – a minority have delusions/hallucinations; *** subjective paresthesia/dysesthesia; **** plaques have an eosinophilic center and pale periphery with surrounding spongiform changes (“florid” and “cluster” plaques); ***** visual (Heidenhain variant), cerebellar (Oppenheimer-Brownell variant), thalamic, and striatal variants. **** it varies when comparing original series with most recent ones.

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of PRNP gene mutations appears to be a sensitive and highly specific way to diagnose GSS. Neuropathology, although less used in practice, can also be useful.

The degree of dementia in GSS varies among affected families and individuals within the same family. Part of the variability of expression of this illness may be due to differences in the underlying PRNP mutation or the associated polymorphisms in codon 12915.

3. Fatal familial insomnia (FFI)

FFI was first identified in Italian families, but kindreds have now been reported throughout the world. Although rarely, sporadic cases are also described. Disease onset is earlier and duration is shorter in those who are homozygous for methionine at codon 129. It is a rapidly fatal disease in which patients characteristically develop progressive insomnia with loss of the normal circadian pattern, along with dysautonomia and endocrine disturbances. Patients characteristically develop progressive insomnia with loss of the normal circadian sleep-activity pattern, which may manifest as a dream-like confusional state during waking hours. Inattention, impaired concentration and memory, confusion, and hallucinations are frequent, but overt dementia is rare16. Methionine-homozygous patients are more likely to have hallucinations and myoclonus as prominent disease features, while methionine-heterozygous patients are more likely to develop early problems with ataxia, bulbar signs, and nystagmus.

Dysautonomia is characterized by hyperhidrosis, hyperthermia, tachycardia, and hypertension. Endocrine disturbances include decreased ACTH secretion, increases in cortisol secretion, and loss of the normal diurnal variations in levels of growth hormone, melatonin, and prolactin. Fluorodeoxyglucose PET showing decreased glucose utilization in the thalamus may be detectable even before the development of clinical symptoms. Sleep studies demonstrate a dramatic reduction in total sleep time and disruption of the normal sleep architecture. Genetic studies are now the diagnostic procedure of choice for diagnosis of this condition. Most cases are associated with the D178N PRNP gene mutation17. Spongiform degeneration, a characteristic feature of most of the human prion diseases, is rarely detected in FFI, particularly in those with the methionine-homozygous genotype. Neuronal loss and gliosis that is maximal within the thalamus is a consistent finding. These changes can also occur in other regions of the brain as well as in the cerebellar cortex, cerebellar nuclei, and olivary nuclei18.

4. Creutzfeldt-Jakob disease (CJD) and its variants

CJD is the most frequent of the human prion diseases. CJD most often occurs as a sporadic disorder (sCJD) although familial forms (fCJD) have been described. It is clinically manifested by a rapidly progressive mental deterioration, often with behavioral abnormalities, and myoclonus. Eight-five to ninety-five percent of CJD cases are sporadic, while 5 to 15 percent are due to fCJD; iCJD generally accounts for less than 1 percent. Family history of CJD, a medical history of psychosis, history of multiple surgical procedures and residence for more than 10 years on a farm were all significant risk factors for sCJD. No study so far documented an increased risk of sCJD with receipt of blood products19.

Variant CJD (vCJD) is a distinct disorder with clinical, diagnostic and pathological features different from sCJD20. It was first reported in 1996 and since then around 230 cases have been described. The vCJD represents bovine-to-human transmission of BSE, most patients acquiring the disorder through ingestion of infected meat products. The removal of organic solvents, which inactivate PrPSc, from the rendering process for bovine offal, and the subsequent use of the offal as a component of feed for cattle has been hypothesized to be a mechanism for amplifying the epidemic in animals. The source of BSE remains unclear. The first cases were recognized in 1986. Theories of its origin include the transmission of either sheep scrapie or another prion disease to cattle via contaminated feed. An intrinsic genetic event in cattle seems less likely21.

According to international regulations, a country may be considered a minimal-risk for BSE, if it has less than two BSE cases/million cattle over 24 months of age during each of the previous four consecutive years. Brazil is recognized as having a negligible BSE risk, i.e. the most favorable category. Just one case of BSE has been described in Brazil so far (2012) but the dead animal was destroyed and did not enter the food or feed chain. Updated information on the number of BSE cases reported throughout the world in imported or indigenous cattle is available online from the OIE website (www.oie.int).

The US Food and Drug Administration (FDA) adopted a policy that a prospective blood donor be indefinitely deferred if he or she had lived for more than six months in the United Kingdom during the peak years of BSE (1981 through 1996). This policy went into effect in April, 2000, to attempt to balance increased safety against decreased blood availability. There is no evidence of vertical transmission (mother to child) of vCJD, although the potentially long incubation period for this mechanism makes it difficult to exclude this possibility definitively22, 23.

Iatrogenic CJD (iCJD) has followed administration of cadaveric human pituitary hormones, dural graft transplants, use of dural mater in radiographic embolization procedures, corneal transplants, liver transplants, and the use of contaminated neurosurgical instruments or stereotactic depth electrodes. No definite cases of transfusion-associated CJD are known to have occurred, although transfusion-related variant CJD has been described. The incubation period for iCJD is unknown and probably depends upon the mode of transmission. One study estimated a mean time of 9 to 10 years based upon mathematical models of the incubation time for iCJD.
acquired after administration of human growth hormone in a population. CJD infection in health care workers is extremely rare. Physical contact with CJD patients entails no risk of transmission and special precautions are not required in their care. However, special precautions should be employed in the handling of CSF as well as biopsy tissue; all materials and instruments used must be decontaminated according to established protocols.

Other autoimmune, infectious, malignant, and toxic-metabolic etiologies should be considered in the differential diagnosis of CJD.

While brain biopsy is the gold standard test for diagnosis, it is often unnecessary for CJD. A typical clinical presentation with corroborating findings on MRI, EEG, and CSF are usually sufficient to exclude other causes and establish a probable diagnosis.

One feature that distinguishes vCJD from sCJD is its prominent tropism for lymphoid organs such as the tonsils. Analysis of PrP extracted from tonsil biopsy tissue appears to provide a sensitive and specific method for the diagnosis of vCJD in the appropriate clinical context. On the other hand, detection of the 14-3-3 protein in CSF is not a sensitive marker for vCJD.

In sCJD MRI typically shows abnormal signal in the putamen and head of the caudate. Sensitivity and specificity for typical MRI findings range between 83 to 92 percent and 87 to 95 percent respectively. A finding of periodic sharp wave complexes (PSWC) on EEG has a high specificity for the diagnosis of CJD, but a low sensitivity. The 14-3-3 protein test in CSF is a specific test finding for CJD, but its sensitivity can be low, particularly in some molecular subtypes.

Clinical phenotypes of sporadic CJD have been associated with molecular subtypes determined by the PRNP gene codon 129 genotype and the pathologic prion protein (PrPSc) type. The PRNP genotype is homozygous or heterozygous for methionine (M) or valine (V) at codon 129. Using this molecular classification, six clinical phenotypes of sCJD have been described:

- MM1 and MV1 (myoclonic, Heidenhain variant) account for about 70 percent of cases and correlate with the "classic CJD" phenotype of advanced age at onset, a rapidly progressive dementia with early and prominent myoclonus, and a short duration of illness (mean 3.9 months). The MM1 phenotype is the one most commonly associated with periodic sharp wave complexes (PSWC) on electroencephalogram (EEG).
- VV2 (ataxic variant) accounts for 15 percent or less of sCJD and presents with ataxia at onset, often as an isolated feature, late dementia, and a longer duration of illness (mean 7 to 9 months).
- MV2 (Kuru plaque variant) accounts for 9 percent and presents with ataxia, progressive dementia with prominent psychiatric features, and longer duration (mean 17.1 months). The 14-3-3 protein in the CSF is a relatively insensitive marker for the MV2 variant (about 70 percent), and PSWCs are only infrequently seen on EEG.
- MM2 can present as either a thalamic variant or a cortical variant. Some, but not all, patients have a young age at onset, and the disease course is typically long, with a median disease duration of 14 months in one study. The 14-3-3 protein has been reported to be present in 61 to 91 percent of patients with MM2, and PSWCs on EEG are more often absent than in other MM and MV subtypes. The clinical features of MM2 type sCJD may resemble those of variant CJD. The thalamic MM2 variant accounts for 2 percent of cases, and mean disease duration is 15.6 months. Insomnia, psychomotor hyperactivity, ataxia, and cognitive impairment are the predominate manifestations, and this phenotype resembles that of FFI. The cortical MM2 variant accounts for 2 percent of cases, with a mean disease duration of 15.7 months. Dementia is the predominate manifestation, while cerebellar and visual signs are rarely described at presentation.
- VV1 accounts for 1 percent of cases and is notable for progressive dementia and longer duration (mean 15.3 months). A case series of nine patients with this subtype confirmed the slower, more prolonged course (median 21 months). All patients had elevated CSF levels of the 14-3-3 protein, but none had PSWCs on EEG, and cortical rather than basal ganglia abnormalities were more common on MRI.
- PSWCs are helpful in the differentiation of sCJD from other prion disease. For example, PSWCs are occasionally found in patients with FCJD, although PSWCs are found more commonly in patients with FCJD who have the codon 200 mutation; PSWCs are not found in patients with vCJD, kuru, Gerstmann-Sträussler-Scheinker syndrome, or fatal familial insomnia; PSWCs may be more commonly absent in the thalamic variant of MM2 sCJD, as well as the MV2 and VV2 subtypes and in iatrogenic CJD.
- PSWCs may not be recorded in the initial stages of the illness. The probability of recording PSWCs corresponds to the amount of neuronal loss, and serial EEG recording may be useful in patients suspected of having sCJD when initial EEG recordings are negative. PSWCs typically disappear in later stages of sCJD, which is characterized by low voltage activity followed by electrocerebral inactivity. It must be remembered that drugs such as barbiturates and benzodiazepines can mask PSWCs.

The 14-3-3 protein has been seen as a sensitive and specific diagnostic test for sCJD. In one study, CSF 14-3-3 protein had a positive predictive value of 95 percent for patients with pathologically definite and probable sCJD. However, subsequent reports have found somewhat lower sensitivities and specificities of 53 to 88 percent. In addition, "false positive" elevations in CSF 14-3-3 have been noted in patients with herpes simplex encephalitis, hypoxic encephalopathy, cerebr al metastases, paraneoplastic disease, and metabolic...
encephalopathies. It seems that the protein may be a marker of brain cell death rather than CJD. Studies have suggested that the 14-3-3 protein test may be helpful for diagnosis of the classical subtypes of sCJD but may be falsely negative for the nonclassical subtypes. Taken together, these studies suggest that detection of CSF 14-3-3 protein in CJD should be considered an adjunctive rather than absolute test for the diagnosis of prion diseases. A negative test does not exclude the diagnosis, especially in cases of possible CJD or nonclassical sCJD, and a positive result can occur in nonprion diseases. However, a positive test increases the probability of CJD when other clinical features are suggestive but not diagnostic. Pathological studies of brain material to detect protease resistant PrPSc remain the gold standard for the diagnosis of prion diseases.

A variety of other CSF diagnostic tests have been reported in small series (S100 protein, neuron specific enolase, thymosin β4, and tau protein). Further studies are however necessary to evaluate their real usefulness for CJD diagnosis. Prion protein diagnostic assays performed on blood samples, are in development and in one case series, elevated plasma levels of several acute phase reactants were noted in patients with CJD. All of these tests are of unproven diagnostic utility at present.

Routine laboratory studies are normal in CJD with the occasional exception of liver function tests. The CSF contains no cells and usually has normal glucose. An elevated CSF protein may occur in about 40 percent of patients.

**Treatment**

Prion diseases are always fatal, regardless of any current treatment effort. Care for patients with prion disease is therefore mainly supportive. Isolated case reports of stabilization or improvement following treatment with amantadine, acyclovir, interferons, polyamines, vidarabine, and me thioprinol have not been replicated.

Quinacrine and chlorpromazine, which were found to inhibit PrPSc formation in a cultured neuroblastoma cell line (ScN2a) chronically infected with prions, also failed to show any benefit when used in humans.

Finally, Flupirtine maleate, a centrally acting nonopioid analgesic that has displayed cytoprotective activity in vitro in neurons inoculated with a prion protein fragment did not show significant effect on survival time compared with placebo. However, patients performed significantly better on the cognitive part of the Alzheimer Disease Assessment Scale (ADAS-Cog) and on the Mini Mental Status Examination, but the difference did not reach statistical significance. Caregiver’s impressions were also significantly better in the flupirtine-treated group.

Laboratory models used for studying prion diseases may assist in the testing of new agents. The scientific advances in the understanding of the molecular pathogenesis of prion diseases are expected to lead to the identification of new targets for therapy [v.g., iP13, a peptide that can break a beta-sheet conformation; depletion of endogenous PrPSc by molecular methods; induction of immune activation through the exposure of a prion protein epitope that is selectively exposed in the pathologic conformation; anti-PrP monoclonal antibodies; adenovirus vector platforms that express PrP single-chain fragment (scFv) antibodies]. As already mentioned, however, at this moment, prionic diseases are incurable and invariably fatal.

**References**