

New variant of Creutzfeldt-Jakob (vCJD) disease and other human prion diseases under epidemiological surveillance in Brazil

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Abstract – To increase the timeliness of detection of human cases of the new variant of Creutzfeldt-Jakob disease (vCJD) and to reduce the risk of transmission, the Brazilian Ministry of Health has established and standardized rules and control measures. These include the definition of criteria for suspect cases, reporting, monitoring, and control measures for illness prevention and transmission. Guidelines to be used by the team of health care staff were published and distributed to health workers. A detailed proposal for a simplified system of surveillance for prion diseases was developed and mandatory reporting introduced. Additional effort is necessary to increase vCJD case detection, thus making it necessary to establish a partnership with health care services for best identification of suspected cases and dissemination of information to all involved in the service dealing with vCJD investigation. **Key words:** prion, Creutzfeldt-Jakob disease, new variant Creutzfeldt-Jakob disease, epidemiological surveillance.

Vigilância epidemiológica da nova variante da doença de Creutzfeldt-Jakob (vDCJ) e de outras doenças priônicas no Brasil

Resumo – Com o objetivo de detectar de maneira oportuna casos humanos da nova variante da Doença de Creutzfeldt-Jakob (vDCJ) e de reduzir o risco de transmissão da doença, o Ministério da Saúde (MS) vem estabelecendo e padronizando normas e medidas de controle. Estas incluem critérios de suspeita diagnóstica, notificação, monitoramento e medidas de prevenção da doença e seus mecanismos de transmissão. Procedimentos a serem adotados pela área de assistência à saúde também foram produzidos e divulgados. Desenvolveu-se uma proposta detalhada do Sistema Simplificado de Vigilância Epidemiológica das Doenças Priônicas, estabelecendo a compulsoriedade de sua notificação. Muito esforço ainda será necessário para efetiva e rotineira captação da ocorrência de um caso suspeito de vDCJ, por isso faz-se necessário o estabelecimento de uma parceria com os profissionais da assistência por serem estes os que têm a capacidade de identificar suspeitos e remeter a informação a todos aqueles que devem conhecê-la.

Palavras-chave: prion, doença Creutzfeldt-Jakob, nova variante da doença de Creutzfeldt-Jakob, vigilância epidemiológica.

In view of the recent emergence of the new variant of Creutzfeldt-Jakob Disease (vCJD) in humans, along with its social and economic repercussions, the Brazilian Ministry of Health devised specific activities directed toward prevention of CJD in 2001, by commissioning a Task Force with the following purposes: to produce a report on CJD, to standardize the criteria for suspect cases, to standardize notification and monitoring, to suggest measures to reduce

the risk of disease transmission within the country through health related products and procedure adopted by health care services, and to provide useful information for the institutions concerned, as well as for the community.¹ To this end, resolutions were published adopting control measures, which have been constantly updated in the light of the latest scientific knowledge.² The range of health related products based on raw materials extracted from animals,

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including bovine, sheep, goat and buffalo species, in addition to wild ruminants is broad. Materials derived from ruminants are used as components in the production of medicines, cosmetics and other health related products.³

Examples of health related products made from materials of animal origin include: heparin, glycerine, griseofulvin, insulin, magnesium stearate, stearin and polysorbate. For import of such products, ANVISA (the National Health Regulatory Agency) has established several legal requirements based on the potential degree of infectivity of animal tissue being imported and the risk attributed to the country of origin, defined by the number of infected cases identified in the region.³

ANVISA has published two resolutions: RDC 305, of November 14, 2002 and RDC 68 dated March 28, 2003.⁴ The latter establishes conditions for importing, trading, and exposure to consumption of these products while the second measure clarifies rules and procedures concerning the proper processing of materials used in patients with clinical suspicion of CJD or vCJD; biosafety procedures for handling of patients, samples and other materials potentially contaminated with CJD or vCJD agent; procedures for the handling of corpses; relative infectivity of the tissues and the body fluids of animals, as well as definitions for those areas running a geographic risk of transmission. Information on these measures is available at: <http://www.gov.br/vacalouca/index.htm>.

In this same period, a few possible suspect CJD cases were reported to the Health Surveillance Secretariat/Ministry of Health (SVS/MS). At this time however, there was no surveillance protocol in place. Therefore, in December 2004, the Technical Advisory Group for Prion Diseases (GTA – Prions) – was commissioned comprising members of the “National Health Regulatory Agency” (ANVISA), and the Brazilian association of neurologists (Academia Brasileira de Neurologia). GTA-Prions developed a detailed proposal for the establishment of the “Simplified System for the Surveillance of Prion Diseases”. The implementation of the system is currently directed towards the timely discovery of possible cases of Creutzfeldt-Jakob (CJD) Disease and its variant (vCJD); aiming to reduce under-reporting of prion diseases in Brazil; to better understand the epidemiological profile of this illness throughout the country; to enable epidemiological, clinical and laboratory investigation of reported cases; to adopt individual and collective protective measures upon detection of new cases of such diseases; and to deploy possible prevention and control measures in the event of cases being identified within Brazilian territory.

At the beginning of 2005, the Technical Advisory Group for Human Prion Diseases (GTA-Prions) put forward the following components of the surveillance system: a notification form with case definitions of the clinical categories of prion diseases; a protocol for epidemiological, clinical and laboratory investigation of notified cases; the descrip-

tion of epidemiological, clinical and laboratorial information flows within the system; the definition of the reference clinics where the system will be implemented, and the identification of laboratories that are equipped to carry out the tests proposed in the protocol.

The National Seminar on Human Prion Diseases was held on June 8, 2005, with the participation of members of the Ministry of Agriculture, proposed surveillance actions for the Bovine Spongiform Encephalopathies, (BSE) and had the main objective of submitting the surveillance system proposal to neurologists practicing at state level and to the states’ epidemiological surveillance units. In August the same year, a meeting was held by the GTA-Prion (TAG) to incorporate suggestions presented at the seminar.

On July 07, 2005, the Ministry of Health classified CJD as a disease requiring mandatory notification through Regulation No. 33/2005, making the Simplified System of Epidemiological Surveillance of Human Prion Diseases in Brazil official.⁵ The inclusion of the disease onto the lists of diseases for which suspect cases must be notified to health surveillance services to allow further mandatory investigation, raised awareness of the disease to health authorities who then began reporting cases in many Brazilian states.

From August 2005 through December 2006, 30 suspected cases of CJD were reported to SVS/MS, in 12 Brazilian states.

The system still has some limitations, mainly concerning laboratory diagnosis and the very nature of Human Prion Diseases.⁵ The complexity of some of the required procedures (including biosafety rules), and consequently the difficulty in establishing a steady flow of samples can delay definitive diagnosis, and compromise the outcome of epidemiological investigations.

Despite the difficulties outlined, the state surveillance services have successfully adapted their routines during investigations of suspected cases of prion disease and have managed, with the assistance of reference laboratories and neurology services involved, to notify a number several of cases given the rareness of the disease and unprecedented nature of the proposal.

With regard to laboratory surveillance, collaboration amongst research centers has been pursued, to devise possible, often highly complex, methodologies. In this context, detection of the 14-3-3 protein achieved by the Laboratory of Hospital das Clínicas/School of Medicine of São Paulo University (HCFMUSP), has greatly aided diagnosis of the sporadic form of the disease, currently representing the sole parametric parameter included in the criteria for probable diagnosis of vCJD, and presents greater than or equal sensitivity and specificity than typical electroencephalogram. In spite of current advances in diagnosing the disease, it is recommended that other tests available for detection should be used in conjunction.

Molecular diagnosis is being carried out by the Ludwig Institute, through purification of the DNA obtained after leukocyte separation. Direct sequencing is performed us-

ing High Resolution Liquid Chromatography (DHPLC). Polymorphism studies and mutation research in the human prion gene (PRNP) can be used as an aid to diagnose CJD, whereby researchers have associated the occurrence of polymorphisms at codon 129 and protease resistant chemical-physical properties of cerebral prion protein (PrP^{Sc}) with the disease. Two PrP^{Sc} strains have also been reported, namely Types 1 and 2, along with three possible genotypes at codon 129 (Methione homozygous (MM), valine homozygous (VV) and heterozygous), responsible for 6 sub-types of the disease. The majority of sporadic CJD cases are MM1 or MV1.

Concerning histopathological diagnoses, sending of material to Rio de Janeiro Federal University laboratory is in place, where macroscopic studies of the brain, frontal lobe fragments, basal ganglia, temporal lobe, occipital lobe, mesencephalon, bridge, bulb and cerebellum are being carried out. The diagnosis is considered positive for CJD when the following 3 pathognomic characteristics of the disease are identified: Spongiosis, neuronal loss and gliosis. The microscopic aspect reveals spongiosis of the cortex due to reactive astrocytic gliosis, in proportion to the degree of neuronal loss.

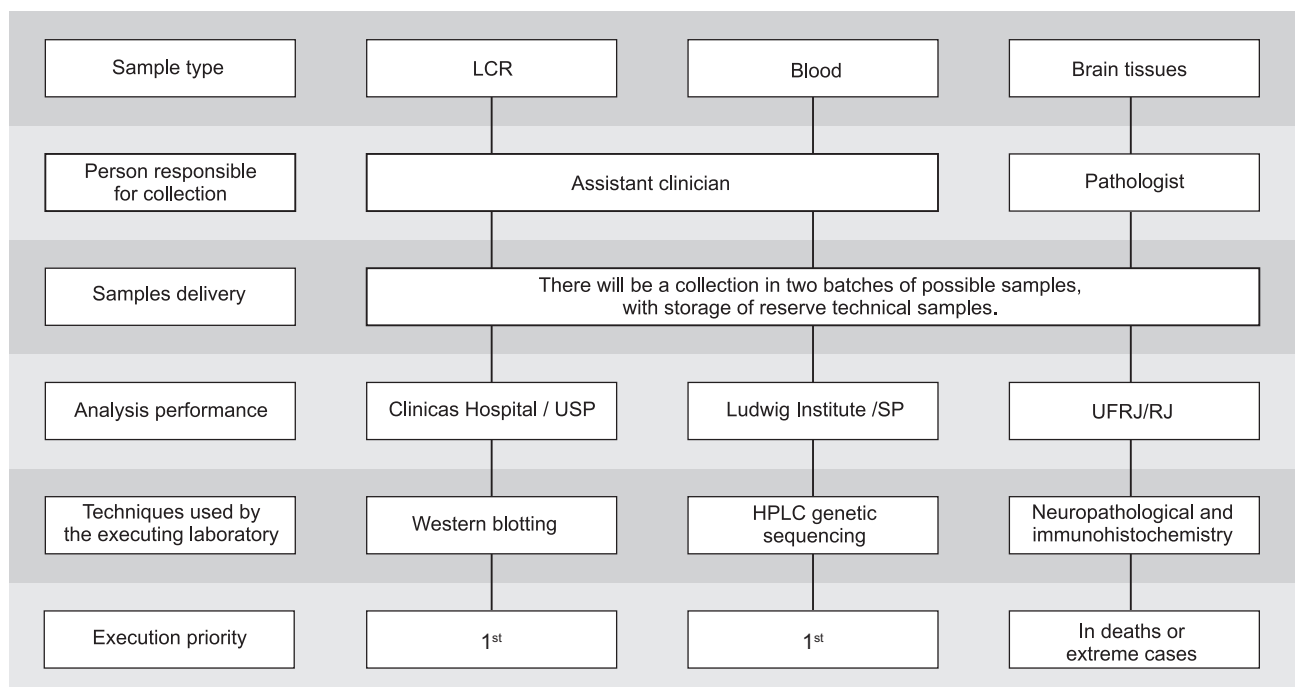
Constant improvements in surveillance activities are aimed primarily at increasing the sensitivity of the system for early detection of vCJD cases, in view of the burden these place on the Brazilian health system. The decision to include other prion disease in the system stems from the syndromic features displayed by these pathologies, particularly in their initial stages, which make the devising of a notification form exclusively for suspected cases of the new variant unrealistic. Thus, all prion diseases are reported.

At a later stage, cases not meeting the criteria for vCJD are excluded and may or may not call for control responses, in addition to the natural interest for clinical and epidemiological research.

The epidemiological notification form and flow of delivery of samples to the laboratory are shown below.

References

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5. Despacho no. 33/2005 de 28 de junho de 2005, Altera o Despacho Normativo n.º 7/2005, de 1 de Fevereiro, que estabelece os requisitos mínimos para as boas condições agrícolas e ambientais. Seleção de legislação – Diário da República. Edição 118/05, 28 de Junho de 2005. Brasília, DF, Brasil.



**NOTIFICATION FORM
PRION DISEASES**

N°

Possible Creutzfeldt Jakob (CJD): Cognitive Decline is Rapidly Progressive (duration of symptoms shorter than two years). Presence of at least two of the following signs/symptoms: Movement, visual or cerebral disturbances. Pyramidal or extrapyramidal signs or akinetic Mutism.
Probable CJD: criteria utilized for possible CJD, followed by electroencephalogram (EEG) with periodic activity or presence of the protein 14-3-3 in cerebrospinal fluid (CSF) or suggestive alterations on magnetic resonance imaging.
Defined CJD: Neuropathological diagnosis through identification of prion protein.
 New CJD Variant: Early onset of the disease, initial psychiatric disorders, epidemiological link (international travel, history of beef consumption abroad, age group.

General details	1 Type of Notification 2 - Individual	
	2 Affliction/Disease	3 Date of Notification
	4 State (Abbrev.)	5 Municipal District of Notification
	6 Health Unit (or other Notification Source) Code	
		7 Date of First Symptoms
		IBGE (Census) Code

Individual notification	8 Name of Patient		9 Date of Birth	
	10 or Age <input type="checkbox"/> 1 - Hour <input type="checkbox"/> 2 - Day <input type="checkbox"/> 3 - Month <input type="checkbox"/> 4 - Year	11 Sex <input type="checkbox"/> M - Male <input type="checkbox"/> F - Female <input type="checkbox"/> 1 - Ignored	12 Expectant mothers <input type="checkbox"/> 1 - 1 st 3 months 2 - 2 nd 3 months 3 - 3 rd 3 months 4 - Gestational age nored 5 - No 6 - Not applicable 9 - Ignored	13 Race/Color <input type="checkbox"/> 1 - White 2 - Black 3 - Yellow 4 - Mulatto 5 - Indigenous 9 - Ignored
	14 Schooling <input type="checkbox"/> 0 - Illiterate; 1 - 1 st to 4 th grade incomplete of Primary School; 2 - 2 nd -4 th grade of Primary completed; 3 - 5 th to 8 th grade incomplete of Primary; 4 - Primary schooling completed; 5 - Secondary schooling not completed; 6 - Secondary schooling completed; 7 - Higher education incomplete; 8 - Higher education completed; 9 - Ignored; 10 - Not applicable.			
	15 Number of SUS (NHS) Card	16 Mother's Name		

Address details	17 State (Abbrev.)	18 Municipal District of Abode	IBGE (Census) Code	19 District
	20 District of Residence	21 Address (street name..)		Code
	22 House Number	23 Complement (apartment, house)		24 Geographic Location field 1
	25 Geographic Location field 2	26 Reference Point		27 Zip Code
	28 (Area Code) Phone Number	29 Area <input type="checkbox"/> 1 - Urban 2 - Rural 3 - Sub-urban 9 - Ignored	30 Country (If residing abroad)	

Supplementary Data on Case

31 Criteria for Clinical Suspicion
 1. Possible Creutzfeldt Jakob Disease (CJD) 2. Probable CJD 3. Defined CJD 4. New Variant CJD 5. Other possible Prion Diseases (GSS; IFF)

Clinical Data	32 Date of First Symptoms	33 Occupation
	34 Signs and Symptoms (1 - Yes 2 - No 9 - Not Given)	
	<input type="checkbox"/> Progressive Dementia (less than 2 years)	<input type="checkbox"/> Cerebral Disturbances
	<input type="checkbox"/> Myoclonia	<input type="checkbox"/> Persistent Painful Dysesthesias
	<input type="checkbox"/> Visual Disturbances	<input type="checkbox"/> Ataxia
	<input type="checkbox"/> Pyramidal Signs	<input type="checkbox"/> Psychiatric Disorders
	<input type="checkbox"/> Extrapyramidal Signs	<input type="checkbox"/> Sleep Alterations
	<input type="checkbox"/> Akinetic Mutism	

Epidemiological Aspects	35 Has patient traveled abroad since 1984? <input type="checkbox"/> 1 - Yes 2 - No 9 - Not Given	36 Date of last trip	37 Country
	38 Have any family members presented similar symptoms? <input type="checkbox"/> 1 - Yes 2 - No 9 - Not Given	39 Does patient eat beef or has eaten since 1984? <input type="checkbox"/> 1 - Yes 2 - No 9 - Not Given	40 Is patient a vegetarian? <input type="checkbox"/> 1 - Yes 2 - No 9 - Not Given
	41 Iatrogenic Exposure. In case of specific iatrogenic exposure: 1 - Yes 2 - No 9 - Not Given		
	<input type="checkbox"/> Dura-mater	<input type="checkbox"/> Cornea Transplant	<input type="checkbox"/> Blood Transfusion
	<input type="checkbox"/> Human Growth Hormone	<input type="checkbox"/> Neurosurgery	

Auxiliary tests	42 EEG <input type="checkbox"/> 1. Normal 2. Typical 3. Atypical <input type="checkbox"/> 9. Non performed	43 Magnetic Resonance: <input type="checkbox"/> 1 - Normal, with diffusion 2 - Normal without diffusion 3 - Typical with diffusion 4 - Other abnormalities <input type="checkbox"/> 5 - Not available 9 - Not performed	
	44 Protein - 14-3-3 in CSF <input type="checkbox"/> 1. Absent 2. Present 3. Inconclusive <input type="checkbox"/> 4. Undergoing analysis 9. Not performed	45 TAU Protein in CSF <input type="checkbox"/> 1. Normal 2. Increased 3. Undergoing analysis <input type="checkbox"/> 9. Not performed	46 Cerebral biopsy with spongiform encephalopathy <input type="checkbox"/> 1. Absent 2. Present 9. Not performed
	47 Necropsy with spongiform encephalopathy <input type="checkbox"/> 1. Absent 2. Present 9. Not performed	48 Immuno-histochemistry showing prion pathological protein <input type="checkbox"/> 1. Negative 2. Positive 3. Undergoing analysis <input type="checkbox"/> 9. Not performed	49 Genetic Analysis (PRNP) <input type="checkbox"/> 1. Mutation present 2. Mutation absent <input type="checkbox"/> 3. Underway 9. Not performed

Conclusion	51 Final Diagnosis _____
	51 Clinical Form <input type="checkbox"/> 1 - Sporadic CJD; 2 - Familial CJD; 3 - Iatrogenic CJD; 4 - Variant CJD; 5 - GSS; 6 - IFF; 7 - Under investigation; 9 - Case excluded (other diagnosis).
	52 Outcome of Case <input type="checkbox"/> 1. Cure 2. Death due to botulism 3. Death due to other causes 9. Not Given

53 Date of Death _____	54 Closing Date _____
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Summary of clinical history

Results of other specific tests for the diagnosis			
Exam	Result	Exam	Result

Investigator	City / Healthy Unity	Health Unity Code _____	
	Name	Function	Signature _____

**FICHA DE NOTIFICAÇÃO
DOENÇAS PRIÔNICAS**

Nº

Doença de Creutzfeldt Jakob (DCJ) possível: Declínio cognitivo rapidamente progressivo (duração dos sintomas menor que dois anos). Presença de pelo menos dois dos seguintes sinais/sintomas: Mioclonias, Distúrbios visuais ou cerebelares, Sinais piramidais ou extrapiramidais ou Mutismo acinético
DCJ provável: Critérios utilizados para DCJ POSSÍVEL, seguido de eletroencefalograma (EEG) com atividade periódica, ou presença da proteína 14-3-3 em líquido cefalorraqueano (LCR), ou alterações sugestivas à ressonância magnética
DCJ definida: Diagnóstico neuropatológico por identificação de proteína priônica
Nova Variante DCJ: Acometimento precoce; transtornos psiquiátricos inaugurais; vínculo epidemiológico

Dados Gerais

1 Tipo de Notificação 1 2 - Individual

2 Agravado/doença **DOENÇAS PRIÔNICAS**

3 Data da Notificação

4 UF 5 Município de Notificação

6 Unidade de Saúde (ou outra fonte notificadora) Código

7 Data dos Primeiros Sintomas

Notificação Individual

8 Nome do Paciente

9 Data de Nascimento

10 (ou) Idade 1 - Hora 2 - Dia 3 - Mês 4 - Ano

11 Sexo M - Masculino F - Feminino 1 - Ignorado

12 Gestante 1 - 1º Trimestre 2 - 2º Trimestre 3 - 3º Trimestre 4 - Idade gestacional Ignorada 5 - Não 6 - Não se aplica 9 - Ignorado

13 Raça/Cor 1 - Branca 2 - Preta 3 - Amarela 4 - Parda 5 - Indígena 9 - Ignorado

14 Escolaridade 0 - Analfabeto; 1 - 1ª a 4ª série incompleta do EF (antigo primário ou 1º grau); 2 - 4ª série completa do EF (antigo primário ou 1º grau); 3 - 5ª à 8ª série incompleta do EF (antigo ginásio ou 1º grau); 4 - Ensino fundamental completo (antigo ginásio ou 1º grau); 5 - Ensino médio incompleto (antigo colegial ou 2º grau); 6 - Ensino médio completo (antigo colegial ou 2º grau); 7 - Educação superior incompleta; 8 - Educação superior completa; 9 - Ignorado; 10 - Não se aplica.

15 Número do Cartão SUS

16 Nome da mãe

Dados de Residência

17 UF 18 Município de Residência

19 Distrito

20 Bairro

21 Logradouro (rua, avenida,...)

22 Número

23 Complemento (apto., casa, ...)

24 Geo campo 1

25 Geo campo 2

26 Ponto de Referência

27 CEP

28 (DDD) Telefone

29 Zona 1 - Urbana 2 - Rural 3 - Periurbana 9 - Ignorado

30 País (se residente fora do Brasil)

Dados Complementares do Caso

31 Critérios de Suspeita Clínica 1. Doença de Creutzfeldt Jakob (DCJ) possível 2. DCJ provável 3. DCJ definida 4. Nova Variante DCJ 5. Outra Doença Priônica Possível (GSS; IFF)

Dados Clínicos

32 Data dos Primeiros Sintomas

33 Ocupação

34 Sinais e Sintomas (1 - Sim 2 - Não 9 - Ignorado)

Demência progressiva (menos de 2 anos) Distúrbios cerebelares Sinais piramidais Transtornos psiquiátricos

Mioclonias Disestesias dolorosas persistentes Sinais extrapiramidais Alterações do sono

Distúrbios visuais Ataxia Mutismo acinético

Aspectos Epidemiológicos

35 Realizou viagem ao exterior após 1984?

36 Data da última viagem

37 País

38 Algum familiar apresentou quadro semelhante? 1 - Sim 2 - Não 9 - Ignorado

39 O paciente come carne bovina ou comeu após 1984? 1 - Sim 2 - Não 9 - Ignorado

40 O paciente é vegetariano? 1 - Sim 2 - Não 9 - Ignorado

41 Exposição iatrogênica (1 - Sim 2 - Não 9 - Ignorado) Em caso de exposição iatrogênica especifique:

Dura-máter Transplante de córneas Sinais piramidais Transfusão de sangue

Hormônio do crescimento humano Neurocirurgias Sinais extrapiramidais

Resultados Laboratoriais	42	EEG	<input type="checkbox"/> 1. Normal 2. Típico 3. Atípico <input type="checkbox"/> 9. Não realizada	43	Ressonância magnética	<input type="checkbox"/> 1 - Normal, com difusão 2 - Normal, sem difusão 3 - Típica com difusão 4 - Outras anormalidades <input type="checkbox"/> 5 - Não disponível 9 - Não realizada
	44	Proteína 14-3-3 no LCR	<input type="checkbox"/> 1. Ausente 2. Presente 3. Inconclusivo <input type="checkbox"/> 9. Não realizada	45	Proteína TAU no LCR	<input type="checkbox"/> 1. Normal 2. Aumentada 3. Em análise <input type="checkbox"/> 9. Não realizada
	46	Biópsia cerebral com encefalopatia espongiforme	<input type="checkbox"/> 1. Ausente 2. Presente 9. Não realizada	47	Necrópsia com encefalopatia espongiforme	<input type="checkbox"/> 1. Ausente 2. Presente 9. Não realizada
	48	Imuno-histoquímica para proteína priônica patológica	<input type="checkbox"/> 1. Negativa 2. Positiva 3. Em análise <input type="checkbox"/> 9. Não realizada	49	Análise genética (PRNP)	<input type="checkbox"/> 1. Presença de mutação 2. Ausência de mutação <input type="checkbox"/> 3. Em andamento 9. Não realizada

Conclusão	51	Diagnóstico Final	
	51	Forma Clínica	<input type="checkbox"/> 1 - DCJ esporádica 2 - DCJ familiar 3 - DCJ iatrogênica 4 - variante DCJ 5 - GSS 6 - IFF 7 - Em investigação 9 - Caso descartado (outro diagnóstico)
	52	Evolução do Caso	<input type="checkbox"/> 1. Cura 2. Óbito por botulismo 3. Óbito por outras causas 9. Ignorado
	53	Data do Óbito	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
	54	Data do Encerramento	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

Resumo da história clínica

Resultado de outros exames específicos para conclusão do caso			
Tipo de Exame	Resultado	Tipo de Exame	Resultado

Investigador	Município/Unidade de Saúde		Cód. da Unid. de Saúde		
	Nome	Função	Assinatura		

