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CJD IN CANADA

HEALTHCARE PROVIDER EDITION

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Mission Statement

The mission of the Prion Diseases Program of the Public Health Agency of Canada is to continually assess, mitigate, and ultimately eliminate risks to human health posed by infectious prion diseases in Canada, through surveillance, laboratory services, research and education.

INTRODUCTION

The **Canadian Creutzfeldt-Jakob Disease Surveillance System (CJDSS)**, which is operated by the Public Health Agency of Canada (PHAC), was established in 1998 as a national surveillance system for human prion diseases, often collectively called Creutzfeldt-Jakob disease (CJD). The main public health goals of the CJDSS are to:

- › identify and characterize all human prion diseases in Canada;
- › better understand their epidemiology and biological causes;
- › develop better options for their rapid and accurate diagnosis;
- › and ultimately protect the health of Canadians by reducing risks of prion disease transmission.

The CJDSS works directly to support patients, families and health-care providers dealing with this difficult disease through education and sharing of information. The CJDSS Healthcare Provider Newsletter is one way in which this is done.

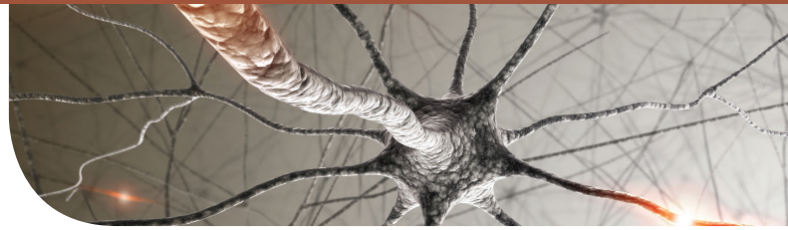
This issue of the CJDSS Healthcare Provider Newsletter includes an update on the number of CJD cases identified in Canada; a brief report on the recent discovery of a second case of variant CJD (vCJD); a feature article on genetics in CJD diagnosis and surveillance; an important announcement concerning new laboratory test options; and a "You Asked Us" section where we respond to some of the questions we frequently receive.



Public Health
Agency of Canada

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publique du Canada

Canada



CJD INFORMATION & UPDATE

(Note that definitions for words highlighted in **bold** can be found in the “Helpful Definitions” box following the article.)

From 1998 to August 31, 2011, the CJDSS has accepted 1179 patient referrals (full case investigations of suspected CJD). Of these, 484 were confirmed by neuropathology or diagnosed as “probable” CJD cases on the basis of non-neuropathology information. For the latest statistics, please visit our website at <http://www.phac-aspc.gc.ca/hcai-iamss/cjd-mcj/cjdss-ssmcj/stats-eng.php>.

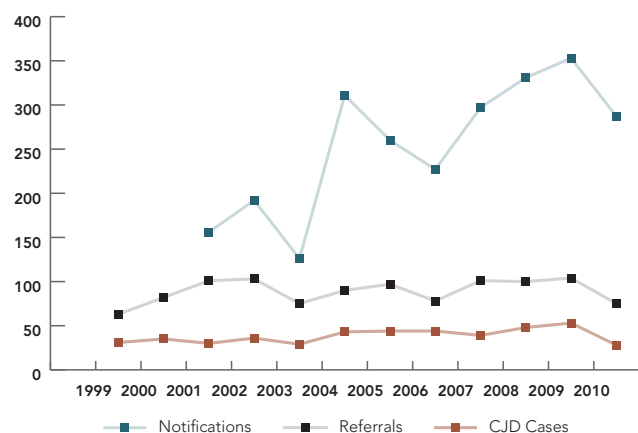
The only way to establish a definite diagnosis of CJD is with neuropathological examination following a brain autopsy (or occasionally a biopsy). Of all cases of CJD identified by the CJDSS to date, 83.5% have been confirmed in this way – one of the highest percentages reached by any country that carries out national CJD surveillance. This is largely attributable to the fact that physicians and other healthcare providers maintain awareness of the disease and collaborate closely with the CJDSS. The CJDSS contributes to this collaborative process by providing laboratory testing services, clinical coordination, expert consultation and logistic support, all of which facilitate timely diagnostic investigation.

Using centrally collected case-specific information, the CJDSS applies formal diagnostic criteria set by the World Health Organization to either exclude a diagnosis of CJD or to assign a possible, probable or definite CJD diagnosis that is then incorporated into a surveillance database. As shown in the graph, each year since 1999 referrals to the CJDSS have been relatively steady, with approximately 60 to 100 patients referred annually. From these referrals the CJDSS has recorded an average of 37.3 definite and probable CJD deaths in Canada per year from 1999 to 2009, corresponding to an average mortality rate of 1.17 cases per million per year. This rate is consistent with CJD mortality rates observed in other countries that performed prospective CJD surveillance over the same period (see <http://www.euocjd.ed.ac.uk/>).

CJD occurs in 3 different forms – **sporadic, genetic, and acquired**. Sporadic CJD accounts for over 90% of CJD cases identified by the CJDSS to date. Approximately 7% of CJD cases in Canada are caused by genetic abnormalities. There have also been 4 iatrogenic cases resulting from accidental transmission during medical procedures. Finally, two cases of variant CJD have been identified in Canadian residents. Variant CJD is the human form of a prion disease of cattle, bovine spongiform encephalopathy (BSE).

The CJDSS depends on sustained collaboration from physicians and other healthcare providers, and will continue to provide support for improved diagnosis and understanding of all suspected cases of CJD in Canada. For more information please visit the CJDSS website at <http://www.phac-aspc.gc.ca/hcai-iamss/cjd-mcj/cjdss-ssmcj/stats-eng.php> or call our toll-free number: 1-888-489-2999.

Notifications, Referrals and CJD Cases by Year of Reporting to the CJDSS



Note: 2009, 2010 and 2011 figures are provisional as information may be incomplete. For CJD incidence by year of death and other information, please refer to our website.

HELPFUL DEFINITIONS

Genetic and **acquired** forms of CJD are attributable to genetic mutations and infection, respectively. **Sporadic** CJD occurs without evidence of either of these causes.





THE SECOND CASE OF VARIANT CJD IN CANADA

In March of 2011, the CJDSS, working closely with Canadian clinicians, identified a probable case of variant Creutzfeldt-Jakob disease (vCJD) in a Canadian resident. Variant CJD is the only known zoonotic human prion disease, resulting mostly from dietary exposure to a feedborne prion disease of cattle, bovine spongiform encephalopathy (BSE, commonly known as “mad cow disease”), that emerged internationally in the 1980s and 1990s. The CJDSS had previously identified only one other case of vCJD (in 2002)¹, and both individuals are believed to have contracted the disease while outside of Canada. Evidence to date also strongly indicates that the most recent case presents no negative implications for the safety of the Canadian food supply, and poses no secondary risks to the health of Canadians. However, the individual’s residence history led to an update of Canada’s deferral criteria for blood donation.

For further information on the second Canadian case of variant CJD, please refer to the original case report² and for information pertaining to blood deferral policies, please visit the Health Canada Deferral Policy Update³ or the Canadian Blood Services website⁴. Readers can also refer to the Héma-Québec website⁵.

Key Article Links

- ¹ First Canadian Case of Variant Creutzfeldt-Jakob Disease (Variant CJD)
<http://www.phac-aspc.gc.ca/cjd-mcj/vcid-ca-eng.php>
- ² 2011 Original CJD Case Report
<http://www.phac-aspc.gc.ca/ccdrw-rmtch/2011/ccdrw-rmtcs1011r-eng.php>
- ³ Health Canada Deferral Policy Update
http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_51-eng.php
- ⁴ Canadian Blood Services website - vCJD Travel Deferral
http://www.blood.ca/CentreApps/Internet/UW_V502_MainEngine.nsf/page/vCJD%20An%20Introduction
- ⁵ Héma-Québec website
<http://www.hema-quebec.qc.ca/donner/don-de-sang/qui-peut-donner-du-sang/creutzfeldt-jakob.fr.html>

GENETICS IN CJD DIAGNOSIS AND SURVEILLANCE

(Note that definitions for words highlighted in **bold** can be found in the “Helpful Definitions” box following the article.)

Genetic variation plays a number of important roles in the biology of human prion diseases, and for this reason the CJDSS requests consent for molecular genetic testing during full case investigations (referrals) of suspected CJD. Some key background information on this facet of CJD diagnosis and surveillance is provided here.

It is estimated that 5–20% of human prion diseases are caused by **mutations** in the **PRNP** gene, and are thus genetically **heritable**¹. All of the more than 40 different known **PRNP alleles** carrying prion disease-causing mutations have been found to date lie within a short segment of the **PRNP** gene that encodes the amino **acid** sequence of the prion protein (PrP). When present, most of these mutations are **dominant** and highly **penetrant** (i.e., highly likely to cause disease), although age of onset can vary widely from early adulthood (or even adolescence) into old age. Thus, in nearly all cases a straightforward **DNA sequence analysis** can effectively rule in or rule

out a genetic cause for a patient’s neuropathologically confirmed prion disease, and can also strongly support a diagnosis of prion disease even in the absence of neuropathological information. Of the total of 484 definite and probable cases of human prion disease identified by the CJDSS in Canada since 1998, 34 (7%) have been linked to such a mutation.

The **PRNP** sequencing result also has strong predictive value for asymptomatic persons who may themselves wish to undergo testing, for example when a **PRNP** mutation has been confirmed in a family member with CJD. In such cases, because mutant **PRNP** alleles are genetically dominant and highly penetrant, any first-degree relative (parent, sibling or child) of a mutation carrier has a 50% probability of also carrying the mutation, and thus developing the disease. Conversely, even if an asymptomatic individual has a relative who carries a **PRNP** mutation, if no mutation is found in that individual their chance of





developing a prion disease reverts to that of developing sporadic CJD (1–2 per million per year). By similar reasoning, if an individual with confirmed CJD is demonstrated to lack *PRNP* mutations – *i.e.*, their disease is deemed to be sporadic – the lifetime risk of CJD for family members is no higher than that of the general population.

Although neuropathological characteristics of genetic prion diseases vary widely depending particularly on the specific *PRNP* mutation present, the most common **clinicopathological** presentation closely resembles that of sporadic CJD. Even when pathology is available, it is therefore not normally possible without genetic analysis to ascertain whether a mutation is present in such cases. However, individuals who exhibit the Gerstmann-Sträussler-Scheinker (GSS) type of neuropathology are almost always found to carry a genetic mutation in *PRNP*. It is therefore possible in some cases to effectively confirm the presence of a *PRNP* mutation by neuropathology alone, although identification of the exact nature of the underlying mutation still requires DNA analysis. GSS and some other genetically caused human prion diseases can be challenging to identify, as clinical presentation may vary; a clear family history may not be elicited; and sometimes *PRNP* mutations can occur *de novo*². The CJDSS therefore suggests that clinicians keep in mind the possibility of genetic prion disease for any undiagnosed case of subacute encephalopathy.

A second important reason to undertake genetic analysis in CJD surveillance relates to the disease-modifying influence of commonly occurring variants at *PRNP* **codon 129**, which may alternately encode either Methionine (M) or

Valine (V) at the corresponding amino acid position (129) in the prion protein. Although – unlike the pathogenic mutations described above – this genetic information is not useful in predicting future risk of an individual developing CJD, when combined with the characteristics of abnormal PrP seen in brain tissue it constitutes a useful marker to help understand the population-level epidemiology of non-genetic prion diseases. Another application of the codon-129 **genotype** arises in the investigation of variant CJD (vCJD), which is the zoonotically transmitted human form of BSE, an epidemic prion disease of cattle that emerged in the United Kingdom in the mid-1980s. All clinical cases of vCJD identified to date worldwide, including the two cases found in Canadian residents in 2002 and 2011, have carried a homozygous MM codon-129 genotype³. Thus, the finding of this genotype in the presence of other features such as clinical presentation and travel history is considered to increase the diagnostic probability of vCJD; conversely, finding either an MV or VV genotype strongly decreases this probability. The same DNA sequence analysis of the *PRNP* gene can be used to ascertain both codon-129 status, and the presence or absence of pathogenic mutations.

As with all genetic diseases, it is crucial that genetic counselling be carried out both before and after testing for heritable forms of CJD, to ensure that patients and family members clearly understand the possible test outcomes as well as their appropriate interpretation, associated risks and benefits, and future implications. The CJDSS asks that caring physicians ensure that these arrangements are made on behalf of participants, but can assist in this process with detailed discussion of the scientific background – please call toll-free: 1-888-489-2999.





HELPFUL DEFINITIONS

A **mutation** is defined broadly in genetics as any change in the sequence of an organism's DNA. In medicine, the term *mutation* usually refers more narrowly to a DNA change that gives rise to a harmful trait.

PRNP is the name of the human gene that encodes the prion protein.

Heritability refers to the property, or degree, of genetic transmissibility of a trait from parent to offspring.

Variant versions of a particular DNA segment that arise by mutation are known as **alleles**.

Amino acids are the biochemical subunits of proteins that are encoded by a corresponding DNA sequence.

In humans, two copies of each gene – one inherited from each parent – are normally present, and these can be identical in DNA sequence or different. A **dominant allele** is defined as a genetic variant that exerts its full effect on a trait whether one or two copies of the variant are present in an individual.

Penetrance is defined as the proportion of individuals carrying a particular genetic variant that consequently express a specific trait.

DNA sequence analysis is defined as determination of the full sequence of nucleotide bases in a specific linear segment of an individual's DNA.

Clinicopathological is a term used to refer to the combination of clinical and pathological features observed in a patient.

A **de novo** mutation is one that is determined to have arisen for the first time in a particular individual.

A **codon** is a 3-nucleotide segment of DNA sequence that encodes an individual amino acid.

An individual's **genotype** refers to their genetic makeup at a particular location in their DNA.

References

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- ² Hinnell C, Coulthart MB, Jansen GH, Cashman NR, Lauzon J, Clark A, Costello F, White C, Midha R, Wiebe S, Furtado S. Gerstmann-Straussler-Scheinker disease due to a novel prion protein gene mutation. *Neurology* 2011 Feb 1;76(5):485-7.
- ³ Bishop MT, Pennington C, Heath CA, Will RG, Knight RS. PRNP variation in UK sporadic and variant Creutzfeldt Jakob disease highlights genetic risk factors and a novel non-synonymous polymorphism. *BMC Medical Genetics* 2009 Dec 26;10:146.





YOU ASKED US

This section provides us with an opportunity to respond to questions that we have received from healthcare professionals dealing with CJD. The CJDSS also invites you to contact us directly if you have any questions, comments or concerns - toll free at 1-888-489-2999 or via email at CJDSS@phac-aspc.gc.ca.

Q. Our unit has been caring for a patient with suspect CJD; is the staff at risk of contracting the disease?

- A.** Scientific evidence has not demonstrated the transmission of the disease through routine health-care practices. However, CJD precautions are taken during surgical procedures involving contact with potentially infectious tissue, when handling samples in laboratories, and during an autopsy. Funeral services workers must also take CJD precautions when handling a person's remains. For the World Health Organization tissue infectivity list please refer to the following link – <http://www.who.int/bloodproducts/tablestissueinfectivity.pdf>

Q. What are the diagnostic sensitivity and specificity of the cerebrospinal fluid (CSF) 14-3-3 protein test?

- A.** Testing for an elevated concentration of the 14-3-3 protein in CSF can be helpful in the diagnostic investigation of CJD, particularly sporadic CJD. Based on a cohort of 1000 patients referred for CSF 14-3-3 testing between 2004 and 2010, the CJDSS has estimated a diagnostic sensitivity for this protein marker of 0.88 (95% Confidence Interval, 0.81–0.93) and a diagnostic specificity of 0.72 (95% Confidence Interval, 0.69–0.75) for sporadic CJD. These estimates are broadly consistent with those observed by other groups that have studied similar patient populations. While a negative 14-3-3 does not exclude the possibility of CJD, in the absence of neuropathological findings, when combined with other clinical features, a positive test result can change the status of a sporadic CJD diagnosis from possible to probable.

Q. Why is an autopsy the best way to confirm a diagnosis of CJD?

- A.** While other laboratory investigations (14-3-3 protein, MRI and EEG) combined with clinical information can contribute to the diagnosis of CJD, because false-positive and false-negative results can occur, they are insufficient alone to confirm or disconfirm the diagnosis. For this reason, formal case definitions (<http://www.cjd.ed.ac.uk/criteria.htm>) for CJD require confirmation by neuropathology. The procedure consists of a brain-only autopsy because prions (which are believed to be the cause of CJD) mostly accumulate here. The brain autopsy takes place in certain facilities in Canada with appropriate specialized equipment and trained staff.

NOTE: The autopsy can only take place with informed consent from the patient or their representative. A CJDSS package containing information and consent forms will be sent to you once the referral is made and the patient or their representative agrees to participate in the CJDSS. The CJDSS will organize and pay for all costs of the autopsy.

Q. What are a healthcare provider's responsibilities in reporting CJD for public health purposes?

- A.** All human prion diseases are provincially/territorially reportable and nationally notifiable in Canada. The CJDSS assumes responsibility for national notification, but it is the legal responsibility of the diagnosing healthcare provider to report definite and probable cases of CJD to their Provincial/Territorial Ministry of Health, usually through designated regional public health contacts.



IMPORTANT ANNOUNCEMENT: ADDITIONAL CSF PROTEIN TESTS

The CJDSS Reference Laboratory currently offers accredited laboratory testing for cerebrospinal fluid (CSF) 14-3-3 protein. Effective October 1 2011, ELISA assays for two additional CSF protein markers, tau and S100B, will be added to this laboratory service, and all requests for CSF 14-3-3 testing will elicit a report for all three markers. The 14-3-3 result will continue to be reported as positive/negative, while results for tau and S100B will be reported in units of concentration (pg/mL and ng/mL). Further information on the specifications and performance characteristics of these tests can be obtained by contacting the CJDSS toll-free at 1-888-489-2999, or the CJDSS Reference Laboratory at 204-789-6078 or nml.cjd@phac-aspc.gc.ca.

CONSENT FORM FOR DONATION OF BIOLOGICAL MATERIALS

To support its various surveillance activities, the CJDSS receives specimens of blood, brain tissue and cerebrospinal fluid (CSF) to conduct laboratory tests on persons who are suspected of having CJD. These types of specimens are very valuable in advancing prion disease research, and are often difficult to obtain through alternative means. Research involving unused portions of these specimens may lead to improved diagnostic tests, a better understanding of the causes of CJD, and better ways to manage public health risks.

All participants or their representatives are eligible to donate these specimens for use in future research by signing the Donation of Biological Materials for Research consent form. The CJDSS asks for the collaboration of healthcare providers in the administration of these consent forms. If someone requires assistance in completing these forms or they need more information, please have them call 1-888-489-2999. The CJDSS is very grateful for your cooperation.





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