RESOURCES

Why Do Surveillance of Progressive Intellectual and Neurological Disorders (PIND) in the Paediatric Population?

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The surveillance of progressive intellectual and neurological deterioration (PIND) in the paediatric population is an arm of the Creutzfeldt-Jakob disease (CJD) surveillance program. Its purpose is to assure complete ascertainment of this rare disease by examining a population of paediatric patients with a similar presentation, mainly progressive intellectual and neurological deterioration. The secondary purpose of this expanded surveillance is to obtain much needed data on the frequency of these disorders in the Canadian population.

To be included in this surveillance study, the patient must be 18 years or less. There must be documented evidence of loss of intellectual (cognitive or developmental skills) and progressive neurological symptoms (loss of motor skills). Patients with static disorders associated with mental retardation, chronic seizure disorders, chromosomal abnormalities, brain tumors, post-traumatic brain injuries and static encephalopathies due to inherited metabolic disorders are not included in this program.

The recent bovine spongiform encephalopathy or **"mad cow disease"** outbreak in the United Kingdom and its link to variant CJD has raised concern throughout the world, that CJD could have an animal reservoir with potential for transmission to humans. Variant CJD is different in its clinical presentation when compared with the sporadic (classic) and iatrogenic form of this disorder.

The **classic (sporadic) form** presents as a rapidly progressive dementia with stimulus sensitive myoclonus, cortical blindness, pyramidal and extrapyramidal signs, and cerebellar ataxia. Its onset is insidious often with vague presenting symptoms such as depression, fatigue and weight loss. Usual onset of the disorder is late in life, rarely before 30 years of age.

Iatrogenic forms have been reported secondary to injections of growth hormones extracted from cadaver pituitary glands or surgical dural grafts from cadaver donors.

The clinical picture is similar to the sporadic (classic) form of CJD except that its onset can be in adolescents. Recently a case of iatrogenic CJD in an adolescent secondary to cadaver donor dural graft placement has been confirmed in Canada.

Variant CJD has its onset in late adolescence (16 to 18 years). Often the presenting symptoms were vague behavioural changes, followed within a few months by the development of ataxia and choreoathetosis, progressive dementia and myoclonus. Death is within a couple of years. No previous contact with sources of iatrogenic form of CJD can be found. EEG does not show the classic findings of the sporadic form (i.e., generalized periodic complexes). It is often normal or has nonspecific slowing of the background. Pathological examination of the brain demonstrates the spongiform changes and prion protein plaques similar to the findings in the sporadic and iatrogenic forms. The spongiform changes are most evident in basal ganglia and thalamus.

Since 1994, seven cases of variant CJD have been reported to the CJD surveillance program in the United Kingdom. Age of onset varied from 14 to 18 years of age. Death occurred within 36 months.

CJD and variant CJD are part of the prion disorders. These conditions can be transmitted to experimental animals following inoculation or dietary exposure. The transmissible agent is felt to be a prion, proteinogenous infectious particle. These particles can multiply within the host for several months or years, modifying the normal gene product. They are devoid nucleic acid.

The unique characteristic common to these disorders is the aberrant mechanism of prion protein (PrP). PrP is encoded by a single-copy host gene that is presented and expressed to the same extent in a normal host and those who develop the disorder. The gene that encodes is located in the short arm of chromosome 20.

In the disease state, the PrP gene mutates resulting in accumulation of PrP in the brain as PrP plaques. Inherited forms of CJD have been reported with onset late in life. Mutations associated with the inherited prion disease have been found at codons 102, 105, 117, 145, 178, 180, 198, 200, 210, 217, 232 and insertions. Sporadic and iatrogenic CJD have been reported to occur in genetically susceptible individuals homozygous for common protein polymorphism at codon 129 of PrP either methionine or valine. In the new variant CJD, codon 129 has been found to be methionine homozygous; similar to sporadic CJD.

The differential diagnosis of a patient presenting as a progressive neurological and intellectual deterioration depends on the age of presentation and often the gender. The possible etiologies are large and impossible to completely, or even adequately, cover in this type of communication. Basically, it could include the following disease groups: slow viral disorders; metabolic disorders; spongiform encephalopathies; and toxin. Examples of slow viral diseases include subacute sclerosing panencephalitis (SSPE) and acquired immune disease disorder (AIDS). Neurodegenerative metabolic disorders can be divided into those affecting mainly cortical grey matter, white matter or central core. Grey matter disorders often present as seizures and dementia. Juvenile lipofusinosis, adult variant GM2 gangliosidosis, and Lafora Body myoclonic epilepsy

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are examples of this type of disorder. White matter disorders present as spasticity and changes in mentation. Adrenoleukodystrophy and juvenile metachromatic leukodystrophy are examples of white matter disorders. Central core disorders often present as progressive movement disorders. Huntington's Chorea, Hallervorden-Spatz Disease and Wilson Disorder are examples of this type of disorder. More diffuse progressive neurological disorders can be associated with metabolic disorders such as mucopolysaccharidosis and mitochondrial disorders (i.e., MELAS).

Progressive encephalopathies due to exposure to environmental toxin are rare that present with evidence of changes in levels of mentation. Intrathecal use of methotrexate in the treatment of acute lymphoblastic leukemia, post cranial radiation, and heavy metal exposure are possible examples.

To this differentiation diagnostic list, the spongiform encephalopathies must now be added, as variant CJD is a rare new form of this type of disorder. The expansion of the CJD surveillance to include progressive neurological and intellectual deterioration in the paediatric population has occurred in order to ensure ascertainment of this rare condition is complete in Canada.

The secondary goal of PIND surveillance in the paediatric population is to allow for the collection of data about the possible incidence/prevalence of these rare neurological disorders. From this data, the feasibility of undertaking specific intervention studies—either in the form or specific treatment of prevention of the occurrence of the disorder—can be developed. As well, burden of illness profiles could be developed allowing for better advocacy for this group of patients in obtaining the necessary resources for their care and support for their families.

Key Points

- PIND has located a new case of iatrogenic CJD in childhood in Canada.
- CJD-iatrogenic form still occurs in the child and adolescent population.
- Variant CJD occurs in adolescents with a different clinical presentation from the adult sporadic form.
- Variant CJD has features similar to other disorders of progressive intellectual and neurological deterioration in the child and adolescent populations.
- Surveillance data can allow for the development of further interventional studies.