



Congenital myotonic dystrophy

Principal investigator

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Background

Myotonic dystrophy is an autosomal dominant multisystem disorder characterized by muscle weakness and myotonia commonly beginning in early adulthood. The two loci for the disease are described as DM1 (Steinert's disease) and DM2. In DM1, a CTG trinucleotide expansion is on chromosome 19q13.3, while in DM2, a CCTG tetranucleotide expansion is on 3q21. Although the disruptions of these genes, the DMPK and ZNF9 proteins respectively, may contribute to the symptomatology, the primary pathogenesis is felt to be related to the effect of large accumulations of nuclear mutant mRNA.

In DM1, a phenomenon of 'genetic anticipation' can occur with a more severe clinical phenotype and earlier age of onset appearing over subsequent generations, as the unstable trinucleotide repeat carried by the parent, almost always the mother, can expand further through gametogenesis. This leads eventually to an infant with congenital myotonic dystrophy (CMD), who is often the index case establishing the CMD diagnosis in the mother and serving as a focal point for genetic testing for the family. The incidence of CMD is estimated at 0.08 per 1,000 live births but there are no published population-based incidence studies. Risks associated with CMD include polyhydramnios, premature delivery, labour and delivery complications, and need for neonatal resuscitation.

PROTOCOLS



Although CMD can present with a wide range of symptomatology, the infant often has evidence of hypotonia, weakness, feeding difficulties and respiratory failure requiring intubation and ventilation immediately after birth. Reported CMD mortality rates range from 17% to 41% but are based on case series and retrospective reviews of hospital records. In the past, infants ventilated greater than 30 days were thought not to be able to survive and often had withdrawal of care at that point. There are recent reports of ventilator-free survival after prolonged ventilation. Population-based data through national active surveillance is timely, as prospects for treatments are very promising. Because CMD is an RNA disease, fewer obstacles are forecast in finding treatment than with conventional gene disorder. Basic science researchers are currently attempting to find ways to splice the abnormally accumulated nuclear mRNA. The CPSP study of CMD will be an instrumental part of building an accurate knowledge base on which to base management decision and eventually to plan treatment trials.

Methods

With the active participation of over 2,500 paediatricians, paediatric subspecialists, including neonatologists, neurologists and medical geneticists, who respond monthly to the CPSP, the majority of CMD cases will be ascertained due to the severity of the disease.

Objectives

- To determine the incidence and neonatal mortality of CMD in Canada.
- To provide a clear definition of CMD.
- To describe the burden of illness in newborns with CMD, including duration of ventilation and decision to withdraw treatment.
- To identify the relationship between genotype and phenotype in CMD cases.
- To determine the frequency of both the CMD as the index case and the utilization of genetic counseling services by mothers with CMD.

Case definition

Report any children up to the age of three years with a new diagnosis of CMD.

A diagnosis of CMD will be included if children have **both** of the following **clinical and genetic criteria**:

- Symptoms of myotonic dystrophy in the newborn period (≤ 30 days), such as hypotonia, feeding or respiratory difficulties, requiring hospitalization to a ward or to the neonatal intensive care unit for greater than 72 hours.*
- CMD genetic tests confirming an expanded trinucleotide CTG repeat in the DMPK gene in the child or the mother. An expanded CTG repeat size is >200 repeats or E1-4 classification (E1: 200-500; E2: 500-1,000; E3: 1,000-1,500; E4: $>1,500$).

* Infant does not necessarily need to be born during the surveillance period, as a diagnosis confirmed later may clearly show neonatal complications requiring admissions.



Congenital myotonic dystrophy (continued)

Duration

March 2005 to February 2008 (renewable)

Expected number of cases

Approximately 15 incident cases per year are expected.

Ethical approval

Research Ethics Board of the University of Western Ontario

Analysis and publication

The results will be compiled and reported in a descriptive manner. Incidence of CMD will be reported as number of cases per 100,000 live births based on birth cohort figures published by Statistics Canada for the corresponding years of surveillance. The investigators will provide regular feedback to participants and will publish final study results in a peer-reviewed paediatric journal.

Bibliography

Campbell C, Sherlock R, Jacob P, Blayney M. Congenital myotonic dystrophy: Assisted ventilation and outcome. *Pediatrics* 2004;11:811-6

Liquori CL, Ricker K, Moseley ML, et al. Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of ZNF9. *Science* 2001;293:864-7.

Reardon W, Newcombe R, Fenton I, Silbert J, Harper PS. The natural history of congenital myotonic dystrophy: Mortality and long-term clinical aspects. *Arch Dis Child* 1993;68:177-81.

Reardon W, Newcombe R, Fenton I, Silbert J, Harper PS. The natural history of congenital myotonic dystrophy: Mortality and long-term clinical aspects. *Arch Dis Child* 1993;68:177-81.

Volpe JJ. Chapter 19: Neuromuscular disorders: Muscle involvement and restricted disorders. In *Neurology of the Newborn*, 4th ed. WB Saunders Company, Philadelphia USA 2001.