Congenital myotonic dystrophy in a national registry

Patrick Prendergast BSc[1], Sandra Magalhaes BHSc MSc[1], Craig Campbell MD MSc[2]

P Prendergast, S Magalhaes, C Campbell. Congenital myotonic dystrophy in a national registry. Paediatr Child Health 2010;15(8):514-518.

AIM: To describe the neonatal symptoms, developmental problems and chronic multisystem medical morbidities of congenital myotonic dystrophy (CDM) patients registered in the United States National Registry of Myotonic Dystrophy – a disease-specific, self-report program maintained since 2002. Comparisons with the Canadian Paediatric Surveillance Program for CDM are highlighted.
METHODS: Genetically confirmed cases of CDM demonstrating symptoms in the first four weeks of life are described. Patients (or their caregivers) and physicians completed survey information at baseline and annually thereafter.
RESULTS: Twenty-one patients were included (13 male and eight female), ranging from three to 24 years of age. The CTG trinucleotide repeat number ranged from 940 to 2100. Gastrointestinal, pneumonia and cardiac morbidities were most common. No deaths were noted.
CONCLUSIONS: The United States Registry is a valuable resource for clinical research on patients with CDM; however, in contrast with the Canadian Paediatric Surveillance Program, some limitations are identified.

Key Words: *Congenital myotonic dystrophy; Neonatal; Paediatric; Registry; Trinucleotide repeat disorder*

La dystrophie myotonique congénitale dans un registre national de dystrophie myotonique

OBJECTIF : Décrire les symptômes néonatals, les troubles développementaux et les morbidités médicales multisystémiques chroniques des patients atteints de dystrophie myoclonique congénitale (DMC) inscrits dans le *National Registry of Myotonic Dystrophy* des États-Unis, un programme d'autodéclaration de cette maladie tenu depuis 2002. Le registre est comparé au Programme canadien de surveillance pédiatrique sur la DMC.
MÉTHODOLOGIE : Les chercheurs décrivent les cas génétiquement confirmés de DMC démontrant des symptômes pendant les quatre premières semaines de vie. Les patients (ou la personne qui s'occupe d'eux) et les médecins ont rempli le sondage au départ, puis tous les ans par la suite.
RÉSULTATS : Vingt et un patients (13 garçons et huit filles) de trois à 24 ans étaient inclus. L'expansion du triplet de nucléotides CTG se situait entre 940 et 2 100 répétitions. Les morbidités gastro-intestinales, cardiaques et liées à la pneumonie étaient les plus courantes. On n'a constaté aucun décès.
CONCLUSIONS : Le registre des États-Unis est une source précieuse de recherche clinique sur les personnes ayant une DMC, mais par rapport au Programme canadien de surveillance pédiatrique, il comporte certaines limites.

Myotonic dystrophy (DM) is an autosomal dominant, multisystem myopathic disorder associated with two loci, DM1 and DM2 (1). Only DM1 is associated with severe symptoms in the newborn period, a form known as congenital DM (CDM). DM1 is the result of a CTG trinucleotide repeat expansion found rather uniquely in an intron (noncoding) portion of a gene associated with the dystrophia myotonica protein kinase gene. This gene is located on chromosome 19q13.3 and the mutant repeat expansion causes abnormal splicing of a number of premessenger RNA transcripts, leading to a phenotype with muscle weakness, myotonia, cardiac rhythm disturbance and cataracts as the main symptoms (2). A DM phenotype is commonly observed when the CTG repeat size exceeds 50; however, the repeat size in those with CDM is often much larger, typically greater than 1000.

CDM occurs as a result of the process of genetic anticipation. In this process, the unstable trinucleotide repeat (almost always transferred from the mother) can expand during gametogenesis, which is associated with an earlier onset and more severe disease manifestations in the affected infant. The symptoms of CDM are often displayed in utero as decreased fetal movements and polyhydramnios (3). Symptoms observed more consistently at birth include hypotonia, weakness, feeding difficulties and mechanical respiratory failure requiring intubation and ventilation (4). CDM is associated with significant morbidity in the newborn period, and mortality rates as high as 40% have been reported (4).

The prevalence of CDM is estimated to be one per 3500 to 16,000 individuals (5,6); however, no published population-based incidence studies exist. As well, the lack of a clear and consistent case definition of CDM in the medical literature further complicates efforts to accurately record clinical characteristics and outcomes in this population. Two population-based studies are currently being conducted with these issues in mind, but with different objectives. The first study, which is examined in the present article, is maintained by the University of Rochester Medical Center (New York, USA), The National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members (hereon referred to as the United States

[1]*William Singeris National Centre for Myotonic Dystrophy Research;* [2]*Department of Paediatrics, University of Western Ontario, London, Ontario*
Correspondence: Dr Craig Campbell, Section of Paediatric Neurology, Children's Hospital of Western Ontario, 800 Commissioners Road East, London, Ontario N6A 4G5. Telephone 519-685-8332, fax 519-685-8350, e-mail craig.campbell@lhsc.on.ca
Accepted for publication October 20, 2009

[US] Registry). The purpose of the US Registry is to establish an anonymous database on DM and facioscapulohumeral muscular dystrophy clinical and molecular information, and to assist investigators in identifying and recruiting patients into research trials. The US Registry's database is derived from patient-reported forms and retrospective analysis of patient medical records. The second study, the Canadian Paediatric Surveillance Program (CPSP) and natural history cohort (7), aims to determine the incidence and outcome of CDM. This study is specific to CDM and is a prospective natural history cohort study with active surveillance (7). The two studies have similar definitions of CDM; the CDM is defined in the US Registry as an infant with facial or limb muscle weakness in the first four weeks of life, and either positive genetic testing or a mother with definite/probable DM1, whereas the CPSP uses a definition of CDM based on genetic diagnosis and symptoms requiring hospitalization for more than 72 h in the newborn period.

The objective of the present study was to identify patients with CDM in the US registry and to describe this sample of patients. The US registry has one of the largest collection of cases of CDM patients who have had their symptoms verified and have undergone annual follow-up. The discussion will highlight differences between the self-report US registry and the CPSP.

METHOD

The US Registry recruits patients from across the US using a variety of methods. These recruiting methods include the registry's website, the Rochester neuromuscular clinic, muscular dystrophy association clinics, mailings to neurology groups and individual physicians, support groups and disease-related publications. Enrollment is voluntary.

The US Registry consists of information from both the patient and his/her physician. When enrolled, patients provide medical records and are asked to complete a survey known as the patient information form (PIF). This survey is available online through the registry's website (www.urmc.rochester.edu/nihregistry/). A similar survey is mailed annually to all patients and serves to track any changes in their condition. The survey information can be grouped into 12 overall categories. These categories include the following: information about diagnosis, use of assistive devices, signs and symptoms, broken bones and surgery, medications, allergies, sleep problems, other medical problems, treatments or counselling, occupation and employment, education and ethnicity/race. A physician checklist (PCL) collects information to confirm the diagnosis and assign a DM classification. It also provides overlap of information pertaining to initial symptoms, method(s) of diagnosis and family members affected, which also verifies the clinical information reported by the patients.

Because CDM1 and childhood DM1 patients were grouped together in the US Registry database, the following inclusion criteria were used to identify cases of CDM: symptoms evident within the first four weeks of life, and a confirmed genetic diagnosis of DM1 and/or a first-degree relative with genetic confirmation. Both the PIF and the PCL were used to exclude noneligible patients, with the PCL taking priority over the PIF. Anonymous data of 45 CDM and childhood DM1 patients were reviewed. The application of the inclusion criteria outlined above identified 21 patients with CDM. Of the 24 patients excluded, 18 were excluded because initial symptoms were clearly reported after the first month of life. The remaining six patients were excluded due to symptoms that were inconsistent with congenital onset, even when recorded on the PIF as occurring within the first month.

In comparison, the CPSP is conducting active surveillance of incident cases that are identified through surveillance forms sent to more than 2500 paediatricians and paediatric subspecialists monthly, with response rates of more than 80%. A 94% response rate was achieved for completion of follow-up clinical questionnaires. Patients identified in this incidence study are recruited to participate in a five-year natural history cohort focusing on developmental skills, quality of life, medical morbidity and mortality.

Ethics approval (University of Western Ontario, London, Ontario) and approval from the US Registry Steering Committee to examine anonymous information in the database were obtained. The study was funded by the William Singeris National Centre for Myotonic Dystrophy Research (London, Ontario). The information provided by the US Registry in Microsoft Access (Microsoft Corporation, USA) was re-entered into SPSS version 13 (SPSS Inc, USA) and analyzed. Descriptive statistics were also analyzed using SPSS.

RESULTS

The 21 CDM cases included in the present study were born between 1982 and 2003. The mean age at the time of registration in the database for patients was 9.4 years (range three to 24 years of age). Patients consisted of 13 males and eight females. The majority of patients were Caucasian (n=18), in addition to one of Hispanic or Latino ethnicity, one African-American and one Asian. Most of the patients were recruited to the registry via the Internet (n=10) or through a muscular dystrophy association (n=6). Of the 21 patients registered, 13 (62%) had one other family member in the US Registry. Eight patients (38%) were registered in 2002, three (14%) in 2003, six (29%) in 2004, three (14%) in 2005 and one (5%) in 2006. Due to confidentiality, the geographical distribution of cases could not be reported in the results. The US Registry database administrators stated that the northeastern states were over-represented. Regarding the level of education, seven (33%) patients were in elementary school, eight (38%) did not have any formal education and six (29%) did not report an educational level. Occupational information was collected and no patients reported employment; however, only two patients were of employment age.

Diagnosis

Of the 21 patients, 18 cases reported diagnosis at birth or by one year of age. The remaining three cases were diagnosed at three, seven and 18 years of age. Although these latter cases were diagnosed at a later age, all showed signs of weakness

TABLE 1
Symptoms in the neonatal period for 21 children with congenital myotonic dystrophy

Symptoms	n
Low muscle tone/floppiness	13
Respiratory difficulties	4
Swallowing problems	4
Bradycardia	1
Cyanotic	1
Ptosis of the eye	1
Torticollis	1
Congenital diaphragm paralysis	1
Club feet	1
Failure to thrive	1

Some patients had more than one symptom indicated

TABLE 2
Symptoms at time of registration from the patient information form for 21 children with congenital myotonic dystrophy

Symptom	n
Weakness of face	17
Trouble speaking clearly	13
Difficulty walking on toes or heels or ankle weakness	12
Difficulty getting up from the floor, rising from a chair or climbing stairs	11
Trouble with swallowing	10
Difficulty making a tight fist, loss of grip strength or difficulty opening jars	7
Trouble with hands/grip locking up or hand stiffness	6
Racing heart beat, irregular heart beat, palpitations or pacemaker	3
Trouble with breathing or shortness of breath	2
Baldness	1
Cataracts	0

Mean age of entry into the United States Registry was 9.4 years (range three to 24 years)

within the first four weeks of life according to the PCL. Some patients reported diagnosis by multiple physicians; however, the majority of patients were diagnosed by a neurologist (n=15 [71%]) and/or a specialist in a neuromuscular clinic (n=9 [43%]). Only three (14%) were diagnosed by a primary care physician, and none reported self-diagnosis.

A variety of diagnostic methods were used. By far the most common method was genetic testing because 18 (86%) patients reported having DNA testing performed. The medical records of 14 patients submitted by their physician showed that DNA testing was performed and also showed the associated repeat size. The mean (± SD) CTG repeat size was 1528±411), with a range of 940 to 2100. Two of the 21 patients reported having both an electromyography and a muscle biopsy performed diagnostically, while one had electromyography only and one other had a muscle biopsy only. Seven patients (33%) reported receiving genetic counselling to understand more about the familial nature of DM1.

Signs and symptoms

In the neonatal period, the signs and symptoms reported in the US Registry are shown in Table 1. No data were available to determine important birth characteristics such as gestational age, Apgar scores, the resuscitative effort needed, duration of neonatal admission, the need for assisted ventilation or feeding assistance. The symptoms reported by the patients at the time of registration in the US Registry are listed in Table 2. The mean age at registration was 9.4 years, and ranged from three to 24 years of age.

TABLE 3
Comorbidities reported on the patient information form for 21 children with congenital myotonic dystrophy

Medical condition	n
Constipation	6
Pneumonia	4
Gastroesophageal reflux	4
Chronic infections	3
Heart disease	2
Kidney problem	1
Chronic otitis media	1
Vesicoureteral reflux	1
Encopresis and diarrhea	1

Some patients had more than one comorbidity indicated

Morbidity and mortality

More than one-half of the CDM patients reported gastrointestinal disturbance such as constipation (n=6 [29%]), acid reflux (n=4 [19%]) and diarrhea (n=1 [5%]). Other comorbidity problems included pneumonia (n=4 [19%]) and chronic infections (n=3 [14%]). Two patients reported heart disease. Comorbidity data are presented in Table 3. Of note, none of the patients reported having any of the following relevant medical conditions: diabetes, stroke, asthma, thyroid problems, arthritis, stomach ulcers, sexual dysfunction or psychological problems. No deaths were reported in the database. Database administrators confirmed that all patients available for follow-up were living at the time of the present study.

The following medical assistive devices were needed: wheelchairs (n=8 [38%]), ventilators (n=7 [33%]), continuous positive airway pressure or bilevel positive airway pressure (n=7 [33%]), ankle braces (n=7 [33%]), long leg braces (n=4 [19%]), walkers (n=2 [10%]) and canes (n=2 [10%]). No patient reported needing a cardiac pacemaker. All 21 patients reported receiving physiotherapy, while 71% of patients reported receiving occupational and speech therapy as well. One patient received vocational rehabilitation, and none reported receiving psychological counselling.

Sleep problems were assessed in the US Registry PIF by the Epworth Sleepiness Scale (ESS) (8,9). The ESS ranges from 0 (no daytime sleepiness) to 24 (severe sleepiness), with scores greater than 10 indicating excessive daytime sleepiness. ESS scores were available for 11 individuals with CDM and showed a mean score of 7.1 (range one to 21). Three individuals had scores of greater than 10, with one individual (24 years of age) reporting a high chance of dozing under all circumstances except for "sitting and talking to someone". Of the remaining patients, "watching television"

(n=4) and "laying down to rest in the afternoon when circumstances permit" (n=3) were associated with a moderate chance of dozing.

Longitudinal follow-up

Annual completion of the updated PIF includes between one and three years of follow up. After the first year, there was at least one update for 14 (67%) patients. These updates were, in large part, updates on height and weight (11 updates). Six updated the use of assistive devices and four updated their grade in school. By the third year, eight (38%) had at least one update; again, height and weight were most reported (seven updates), with two school grade updates. No data regarding the number of hospitalizations were provided in the database.

DISCUSSION

Examining the CDM cases in the US Registry provided a description of one of the largest recent series of children affected by CDM, in addition to demonstrating the feasibility of using the established US Registry for clinical research in this population. The US Registry has allowed a review of the clinical characteristics of 21 patients ranging from three to 24 years of age, all of whom met the defined criteria for CDM. As expected, all had some element of hypotonia at birth; however, only six patients displayed neonatal respiratory problems or feeding dysfunction. Because hospitalization information was not specifically collected, it is unclear whether these were sufficiently severe to require hospitalization. The symptom severity of this sample, however, is indicated by the fact that 18 of 21 individuals required at least one assistive device, with the majority requiring devices such as wheelchairs, continuous positive airway pressure or bilevel positive airway pressure. Furthermore, we have demonstrated that a substantial amount of health care resources are used by patients with CDM. The need for health care resources is evidenced by the universal need for physical therapy, and the need for speech therapy, occupational therapy and assistive devices in a majority of cases. The lack of psychology intervention raises concern because there is a high rate of attention-deficit hyperactivity disorder and learning difficulties in children with CDM (10); it is important for school-age children with CDM to be academically assessed to optimize their learning environment. Furthermore, it is important to note that genetic testing confirmed the diagnosis in 85% of patients, yet only 33% reported having genetic counselling to accompany the diagnosis, which, given the autosomal dominant familial nature of this disorder, is concerning because affected parents are at risk of having more children with CDM and proper genetic counselling enables them to make informed reproductive choices.

No deaths were identified in registered patients or during the follow-up period. Because the mortality from CDM has been shown to be 25% in the first year of life (11), one would expect some deaths in follow-up of the youngest children entered in the database. This observation may represent an ascertainment bias in the US Registry, given that parents may not register a child who is seriously ill or who died early in the disease. Only one-third report having been engaged in genetic counselling. Genetic counselling is a critical aspect of the care in this population because there is a high risk of CDM in future familial generations. Because the onset of adult DM1 can manifest in mid-life, and in certain cases with mild severity, the child presenting with CDM is often the index case for the family (11). All families and individuals affected with DM1 should be referred for genetic counselling, and then referred to a neuromuscular clinic for appropriate monitoring and management. Overall, there was a low rate of comorbidity (diabetes, cataract, thyroid problems, orthopaedic problems and cardiac abnormalities), which may further reflect ascertainment bias or be due to the young age of the sample. Gastrointestinal problems appeared most prominent, which is consistent with the low tone effects of CDM on the musculature of the gastrointestinal tract. Similarly, the lack of psychological intervention raises concern that either these issues are not reported accurately by caregivers or that patients are not getting appropriate services. There is a high rate of attention-deficit hyperactivity disorder and learning difficulties in the CDM population; it would be uncommon for a child of school age not to have been assessed to optimize their learning environment. Finally, the lack of daytime sleepiness in the sample was not expected, given the self-reported frequency of fatigue and somnolence of 81% reported in studies of childhood DM1 (12). However, the young age of most patients might limit the appropriateness of the ESS in the population.

The current organization of the US Registry offers opportunities to those interested in performing clinical research in CDM or even childhood-onset DM1, by enabling informed patient selection and allowing personal contact with registrants for participation in approved clinical studies. Providing a combined group of CDM and childhood DM1 registrants enabled the identification of CDM cases using the current case definition; however, the US Registry could, without difficulty, apply a clearer definition of CDM to distinquish these subgroups.

Through comprehensive assessment of the acquired data, it is evident that several data elements are not routinely collected by the US Registry, which may be important to comprehensively understand the clinical course of CDM. Although the purpose of the US Registry is that of patient identification for clinical studies, the addition of information regarding neonatal hospitalization (ie, need for a ventilator or feeding tube), developmental milestones and school performance would help researchers more informatively identify subpopulations within the database and provide pilot data to determine the necessity of certain studies in this population. The US Registry requests that a referring physician's note be submitted, which due to confidentiality is not disseminated, and may provide additional information regarding duration of hospitalization and interventions. The inclusion of this clinical information would provide a further level of verification, help to eliminate bias associated with

patient recall and, thus, improve the accuracy of data submitted by a patient.

The ongoing, prospective CPSP and natural history study of CDM (7) aims to determine the incidence of CDM, to document the neonatal morbidity and mortality, and to quantify the genotype-phenotype correlation in CDM. Currently, the study has identified 31 incident cases since the study inception in 2005. A mortality rate of 19% has been noted in this cohort, with five of six deaths occurring within the first month of life. Once the surveillance study is complete, these results will be published.

The greater number of incident CDM cases identified through the initial four years of the CPSP initiative compared with the number of confirmed cases in the US Registry may be due to the passive nature of recruitment of the US Registry. Although it is well recognized that the incidence of DM1 is highest in some Quebec regions (13), this does not likely account for the difference. To improve the breadth of enrollment in the Registry, it may be helpful to create recruitment tools specifically aimed at enrolling children in paediatric neuromuscular clinics and neonatal intensive care units. An additional limiting factor in the complete description of the natural history of the population in the US Registry is that follow-up information was only available for eight of 21 individuals, which limits further understanding of the natural history in the US Registry and raises questions about the feasibility of contacting individuals for research projects.

The US Registry clearly meets its objectives of enabling rapid identification of patients with CDM and other forms of DM for clinical research. Future steps will include contacting CDM patients to determine neonatal medical information, to understand the factors leading to attrition on follow-up PIFs and to enquire whether these persons would consent to clinical studies and under what circumstances. Additional studies may also involve sending questionnaires to parents and siblings of enrolled CDM patients to enquire about the quality of life, developmental milestones, school performance, medical economics and other management issues faced by these families. Finally, there is potential to contact all adult members of the Registry to better appreciate their experiences of CDM within their immediate and extended families, and following up with affected family members to enquire about neonatal care, deaths and long-term therapies.

CONCLUSION

CDM is a rare disease that requires considerable health care resources to effectively manage a child in both medical and psychosocial domains. The information presented adds to the literature of CDM by offering a description of a large cohort of children with CDM, and provides clinicians managing these children with a current understanding of the clinical presentation and course of children with CDM. Some limitations are identified in the US Registry, specific to CDM, which become more evident in contrast with the CPSP CDM program in Canada. Despite this, the US registry is a valuable resource for clinical research.

ACKNOWLEDGEMENT: The authors thank the staff of the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members, specifically Dr R Moxley, for his assistance in working with the US Registry and his helpful comments on the manuscript.

REFERENCES

1. The new nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). The International Myotonic Dystrophy Consortium (IDMC). Neurology 2000;54:1218-21.
2. Schara U, Schoser BG. Myotonic dystrophies type 1 and 2: A summary on current aspects. Semin Pediatr Neurol 2006;13:71-9.
3. Harper PS. Congenital myotonic dystrophy in Britain. I. Clinical aspects. Arch Dis Child 1975;50:505-13.
4. Hageman AT, Gabreels FJ, Liem KD, Renkawek K, Boon JM. Congenital myotonic dystrophy; a report on thirteen cases and a review of the literature. J Neuro Sci 1993;115:95-101.
5. Wesstrom G, Bensch J, Schollin J. Congenital myotonic dystrophy. Incidence, clinical aspects and early prognosis. Acta Paediatrica Scandinavica 1986;75:849-54.
6. Gonzalez de Dios J, Martinez Frias ML, Egues Jimeno J, et al. [Epidemiological study of Steinert's congenital myotonic dystrophy: Dysmorphological characteristics]. Anales Espanoles de Pediatria 1999;51:389-96.
7. Canadian Paediatric Society. Canadian Paediatric Surveillance Program (CPSP): 2004 Results. Health Canada 2004:54.
8. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991;14:540-5.
9. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376-81.
10. Steyaert J, Umans S, Willekens D, et al. A study of the cognitive and psychological profile in 16 children with congenital or juvenile myotonic dystrophy. Clin Gen 1997;52:135-41.
11. Campbell C, Sherlock R, Jacob P, Blayney M. Congenital myotonic dystrophy: Assisted ventilation duration and outcome. Pediatrics 2004;113:811-6.
12. Quera Salva MA, Blumen M, Jacquette A, et al. Sleep disorders in childhood-onset myotonic dystrophy type 1. Neuromuscul Disord 2006;16:564-70.
13. Yotova V, Labuda D, Zietkiewicz E, et al. Anatomy of a founder effect: Myotonic dystrophy in northeastern Quebec. Hum Genet 2005;117:177-87.