



# 5q spinal muscular atrophy



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## Background

Spinal muscular atrophy (SMA) is a progressive neuromuscular disease associated with the degeneration of motor neurons in the spinal cord and brainstem. It is most commonly caused by biallelic mutations of the survival motor neuron gene (*SMN1*) at locus 5q13.2 (also known as 5q SMA); the majority (>95%) of SMA mutations are due to homozygous *SMN1* deletions (1, 2). Higher copy numbers of a nearby *SMN2* gene is associated with a milder phenotype, as it is able to express 10 to 20% of the full-length survival motor neuron (SMN) protein that is essential for diverse cellular functions (3–6). SMA is the leading genetic cause of infant death and the second most common autosomal recessive disorder after cystic fibrosis (7). Based on recent literature, the estimated incidence of SMA is 1 per 11,000 newborns, with a prevalence of 1–2 per 100,000 persons, and a carrier frequency of 1 in 50 people (8, 9).

SMA is clinically classified into five subtypes, based on the age of symptom onset and the maximum attainable gross motor function (see Table 1) (10, 11). SMA type 0 is a rare in utero-onset disease, with reduced fetal movements and severe weakness leading to respiratory insufficiency at birth, and death before six months of age (12). Types I, II, and III are childhood onset diseases; type I constitutes approximately 60% of all SMA at birth, followed by type II (30%), and type III (10%) (8). Patients with type I SMA present before 6 months of age, with significant muscle weakness, hypotonia, and areflexia leading to progressive feeding and respiratory insufficiency; affected infants are not able to sit and often die before their second birthday if untreated (13). Type II SMA children are symptomatic before 18 months of age; they can sit but are unable to stand or walk unassisted; orthopedic (including joint contractures and scoliosis) and respiratory complications are common and the condition can be associated with reduced life expectancy (14). Patients with SMA Type III present after 18 months of age with the ability to walk unassisted; progressive weakness may result in loss of independent ambulation, but a normal life span can be expected. SMA type IV is an uncommon adult form of SMA, with mild weakness and slow disease progression. Notably, children with SMA are cognitively bright and sociable.

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Table 1 – Classification of SMA subtypes based on onset age and clinical characteristics (25)

Type	Age at onset	SMN2 copies	Highest motor function and presenting symptoms	Natural life expectancy
0	Prenatal	1	History of reduced fetal movements, with severe generalized weakness, hypotonia, areflexia, and joint contractures, necessitating respiratory and other medical support at birth.	< 1 month
I	Birth to 6 months	2,3	Unable to sit, hypotonia, progressive symmetric and proximal weakness affecting legs more than arms, with sparing of facial muscles, “frog-leg” posture, head lag, bell-shaped chest, paradoxical breathing pattern, and absent reflexes. Cognition is normal. Feeding and respiratory problems are common; death due to respiratory failure.	< 2 years
II	< 18 months	3,4	Able to sit unsupported but unable to walk, with hypotonia, areflexia, progressive proximal leg more than arm weakness, orthopedic complications (scoliosis, joint contractures), and restrictive lung disease. Cognition is normal.	> 2 years
III	> 18 months	3,4	Able to walk unaided but may lose independent ambulation due to disease progression, with proximal leg more than arm weakness, reduced reflexes, and normal cognition.	Adulthood
IV	> 21 years	≥4	Similar to Type III, can walk unassisted, with mild proximal leg more than arm weakness.	Adulthood

Despite the severity of the disease, previous studies, including a recent 2000–2014 systematic review, have shown that the diagnosis of SMA was often delayed (15, 16). Among the studies reporting both the age at onset and the age at diagnosis, the weighted diagnostic delay was 3.6, 14.3, and 43.6 months for types I, II, and III, respectively (15). The delay was attributed in part to the variable age at onset and severity of SMA, as well as the relative lack of experience among primary care physicians to distinguish SMA from other causes of hypotonia and weakness (17). In addition to causing significant distress for caregivers (18), the delay in diagnosis may also lead to a missed opportunity to maximize the benefits of early treatment (19). Further education of primary care providers and consultant paediatricians may lead to prompt recognition and optimal intervention. Additional strategies, including newborn dried blood spot screening (NBS) based on real-time PCR assays, may also facilitate early diagnosis and treatment of SMA (20, 21). Thus, the United States Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children recommended to the Health and Human Services Secretary that SMA be added to the recommended uniform screening panel in February 2018; however, SMA-NBS is currently not a routine practice in many countries, including Canada (22).

A recent study by Verhaart et al. using a multi-source approach (genetics laboratories, TREAT-NMD Global SMA Patient Registry, and the Care and Trial Sites Registry) estimated the incidence of SMA in Europe to be 1 in 3,900–16,000 live births (9). Importantly, their study suggests that many SMA patients are not registered in specialized



### ***5q spinal muscular atrophy (continued)***

neuromuscular centres and may not have access to necessary health care services, research opportunities, and standard of care. The authors recommended additional population-based study to confirm these findings (9). Currently, the incidence and prevalence of SMA in Canada is unknown.

In June 2017, nusinersen received regulatory approval from Health Canada as a novel treatment for SMA. It works as an antisense oligonucleotide therapy to increase SMN expression from the *SMN2* gene. Other treatment strategies, including vector-based gene replacement and small molecule therapies, are showing early promise in clinical trials (21, 23, 24). With a growing number of therapies being developed and with comprehensive standard of care recommendations being made available (25, 26), it is timely to conduct a large-scale epidemiologic study of SMA.

### **Methods**

This study aims to estimate the minimum annual incidence of SMA using multiple reported sources, including data from: a) the Canadian Paediatric Surveillance Program (CPSP); b) molecular genetics laboratories; and c) neuromuscular clinic physicians through the Canadian Neuromuscular Disease Registry (CNDR).

#### CPSP

Through the established methodology of the CPSP, over 2,800 paediatricians and paediatric subspecialists will be actively surveyed on a monthly basis for any newly diagnosed cases of SMA. Physicians who identify new cases will be asked to complete a clinical questionnaire for each SMA patient.

#### Molecular genetics laboratories in Canada

Genetics laboratories providing clinical *SMN1* gene testing will be identified using publicly available sources, including the Orphanet database of diagnostic laboratories, the laboratory database via GeneTests.org, the Genetic Testing Registry from the National Center for Biotechnology Information, and expert input from the Canadian College of Medical Geneticists and other researchers in Canada. Data from the genetics laboratories will be collected by an online survey to determine the method of *SMN1* testing as well as the number of new patients with a genetically confirmed diagnosis of SMA. The standardized survey will be sent by personalized emails on a quarterly basis to identify the number of positive SMA cases based on biallelic *SMN1* gene mutations during the study period, excluding prenatal cases. The total number of positive cases during the two-year study period will be compared with the numbers obtained in the preceding three years, if available.

#### CNDR

The CNDR is a national, consent-based neuromuscular registry, with over 3,700 participants. It collects patient registration information from individuals diagnosed with neuromuscular diseases, including clinical data from those with SMA. It is a clinic-based registry, and it works closely with 26 affiliated adult and paediatric neuromuscular clinics across the country. The CNDR collects a number of mandatory and highly encouraged items of genetically confirmed SMA patients. More than 180 paediatric and adult SMA patients have been enrolled in CNDR since 2010. The total number of patients with new diagnoses of 5q SMA who are enrolled in the CNDR will be compared to the numbers of



new cases confirmed through the CPSP and the molecular genetics laboratories of Canada, if possible.



### **Case definition**

Report any patient with a new, genetically confirmed case of SMA (Type 0–III) from birth to 18 years of age (up to the 18<sup>th</sup> birthday).

The majority (96%) of 5q SMA cases are due to homozygous deletion of exon 7 (and exon 8) of the *SMN1* gene; mutations of one *SMN1* allele plus a deletion or mutation of *SMN1* on the other allele can be found in the remaining 3–4% of cases.

### **Exclusion criteria**

Exclude patients with other causes of developmental delay, hypotonia, or weakness (such as genetic or acquired causes of myopathies, muscular dystrophies, neuropathies, neuromuscular junction transmission defects, and central nervous system disorders) or non-5q SMA (such as distal SMA, SMA with respiratory distress, and other genetic or acquired motor neuron diseases). See differential diagnosis of SMA under GeneReviews, available via <https://www.ncbi.nlm.nih.gov/books/NBK1352/>.

### **Objectives**

- 1) Determine the minimum incidence rate of children and youth with SMA in Canada
- 2) Describe the age at onset of symptoms and the age at genetic confirmation of disease
- 3) Describe the age, motor function, and health status of SMA patients
- 4) Describe current treatment for SMA patients across Canada, including access to comprehensive neuromuscular clinics, community services, and SMA-specific therapies

### **Duration**

January 2020 to December 2021

### **Expected number of cases**

Based on the number of live births in Canada (393,102 in 2016) and the estimated SMA incidence of 1 per 11,000 newborns, the estimated number of new cases is about 35 per year, including 21 (60%) new cases of SMA Type I.

### **Study limitations**

As with any voluntary reporting surveillance system, the CPSP recognizes that reporting on minimum incidence rates can have limitations, including under-representation of the disease in the population. It is possible that some groups of children will be missed, for example, those who live in rural or remote areas (e.g., children living in northern communities) as they may be less likely to receive timely specialist care. Youth who are approaching transition-to-adult-care age may also be under-represented, as they may be treated by an adult provider in an adult facility. Moreover, case level surveillance data is extracted from patient charts following the clinical encounter. Data elements, including details of history, physical examination, and relevant components of the diagnostic assessment, not collected as part of routine care may be absent from the surveillance totals.



### ***5q spinal muscular atrophy (continued)***

However, surveillance still serves a very important purpose and provides rich clinical data that will allow a better understanding of SMA in Canadian children and youth.

### **Ethical approval**

- University of Calgary Research Ethics Board
- Health Canada and Public Health Agency of Canada's Research Ethics Board

### **Analysis and publications**

Descriptive statistics, including the mean and standard deviation, or median and inter-quartile range, will be used to describe patient characteristics. Frequency tables will be created to summarize data from ordinal or binary measurements. The minimum incidence will be estimated based on the number of newly diagnosed cases of SMA divided by the population of children (e.g., 7,865,720 under 20 years old in 2016) during the two-year study period, as reported by Statistics Canada. If data is available, the birth prevalence will be estimated based on the proportion of newborns (<30 days old) with confirmed SMA during the same study period. Confidence intervals will be calculated based on the Poisson distribution, using standard statistical methods.

Results from the study will be compared with published population-based studies of genetically confirmed SMA cases and studies of carrier rates, which in some cases provide projections of potential cases in the population. The incidence estimates based on carrier screening generally yield higher estimates than population-based studies of observed cases (8).

This study will seek research collaboration with physicians across Canada, including members of the Canadian Paediatric Society, Canadian adult and paediatric neuromuscular physicians, the CNDR, and the Canadian College of Medical Geneticists. Data analysis will begin within six months after study completion, with a peer-reviewed manuscript to be submitted for publication by early 2022. Furthermore, study results will be presented at conferences to facilitate knowledge translation and to promote awareness and policies related to improving the care of patients with SMA. The results will also be shared with the provincial newborn screening committees and the SMA patient support organizations for further engagement and program planning.

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