LETTER TO THE EDITOR

To The Editor

Ontario Newborn Screening for Spinal Muscular Atrophy: The First Year

Keywords: Spinal muscular atrophy, Neonatal screening, Mass screening, Genetics

Spinal muscular atrophy (SMA) is a rare degenerative neuromuscular disorder. SMA is commonly subdivided into types I, II, and III based on the age of symptom onset and the motor milestones achieved[1]. The most common and severe form, type I, presents in infancy with survival beyond the second birthday rare, making SMA the most common genetic cause of childhood mortality.[1] The incidence of SMA is often cited as ~1 in 10,000 births,[2] but large-scale population studies are required to evaluate the disease prevalence in different populations.

SMA is caused by deficiency of the survival motor neuron (SMN) 1 protein due to disruption of the *SMN1* gene. In addition to *SMN1,* there is also a homologous gene, *SMN2* that originated as an inverted duplication centromeric to *SMN1* and is normally present in 0–5 copies. *SMN2* differs from *SMN1* by five translationally silent base pair changes; however, one of these maps to an exonic splice enhancer which leads to exclusion of exon 7 in ~90% of *SMN2* mRNA and degradation of the resulting protein.[1] *SMN2* thus makes ~10% full-length mRNA (compared to *SMN1*)[3]; disease severity (i.e. SMA type) correlates inversely with *SMN2* copy number although the genotype–phenotype correlation is not absolute.

Recently a number of treatments have been developed which greatly improve motor strength, function, and survival of children with SMA.[4] In June 2017, Health Canada approved nusinersen (Spinraza®) and in December 2020, onasemnogene abeparvovec (Zolgensma®) was approved. A third treatment, risdiplam (Evrysdi®) is currently under review. Given the benefit demonstrated with presymptomatic treatment,[4] SMA was naturally considered for newborn screening (NBS) programs that aim to identify and treat diseases prior to symptom onset which is crucial for patient outcomes. SMA has now been added to NBS panels in more than 10 countries on a pilot or permanent basis.[5]

In Ontario, the Newborn Screening Ontario (NSO) Advisory Council reviewed the evidence and recommended that SMA be added to the provincial NBS panel. [6] SMA was included on a pilot basis in January 2020 and on a permanent basis in July 2020. Ontario is the only jurisdiction in Canada screening for SMA at this time. Prior to screening initiation, Ontario newborn screening and pediatric neuromuscular experts recommended that children with biallelic disruption of *SMN1* (deletion or conversion) and four or fewer *SMN2* copies be reported as positive.[6] NSO performs a laboratory-developed first-tier MassARRAY test for the presence of *SMN1*, and a second-tier multiligand probe amplification (MLPA) test for both *SMN1* and *SMN2* copy number on screening dried blood spots (DBS).[5] It was recommended that screen-positive infants undergo confirmatory molecular genetic testing and, in the case of children with 2 or 3 copies of *SMN2*, begin treatment within 16–30 days.[6] Children with four copies of *SMN2* are closely monitored for symptoms with treatment initiated at the first sign of disease.[6]

In the first full year, NSO tested 139,800 infants. Five infants were identified as positive, representing a provincial birth prevalence of 1 in 27,960. This rate is lower than that reported in the literature[1] however, since this data only captures cases over 1 year, a longer ascertainment period will be important. As more jurisdictions begin to include SMA on newborn screening programs, it will also be seen how Ontario's birth prevalence data compares to similar data that will now be collected prospectively in other regions. Notably, no false-positive cases were identified. Additionally, no false negatives have been identified by pediatric neuromuscular specialists caring for children with SMA in the province. Although NSO only reports children with <4 *SMN2* copies, no infants with 0x*SMN1* and >5x*SMN2* copies have been identified. Of the five infants, one had 2x*SMN2*, three had 3x*SMN2,* and one had 4x*SMN2* copies. All infants were referred to a treatment center by a median of 9 days of age (range: 6–15 days) with clinical neuromuscular assessment and confirmatory diagnostic testing in a clinical laboratory completed by median of 13.5 days of age (range: 12–18 days) for children with <3 copies of *SMN2*, and 24 days for the 4 copy SMN2 case (Table 1). At the time of writing, three patients had received disease-modifying treatment at a median age of 24 days of age (range: 18–32 days). This is consistent with the target time window of treatment initiation within 16–30 days of life.[6] We note that case 5 had complicating factors unrelated to NBS which introduced a delay to treatment initiation and that three of the cases had intervening weekends which introduced a 2-day delay in the time from sample receipt to screening result. All three of the treated patients were documented to be clinically asymptomatic at the time of treatment initiation. The family of one patient (3x*SMN2* copies) declined treatment and the sole 4x*SMN2* copy patient remains asymptomatic and continues to be followed as per provincial guidelines.[6] Once the diagnosis of SMA has been confirmed on an independent sample by a diagnostic laboratory and a baseline functional assessment completed by a trained physiotherapist/kinesiologist, an application can be submitted for private insurance and/or to the Ontario Ministry of Health and Long-Term Care's Exceptional Access Program (EAP) for coverage of nusinersen. Although onasemnogene abeparvovec is approved, there is currently no decision regarding reimbursement criteria. Overall, the workflow has been efficient and treatment initiated within the recommended time goals (Table 1).

An analysis of NSO's first year of SMA screening identified at least three modifications that could potentially reduce time to treatment initiation: (1) operation of NSO molecular laboratory on weekends; (2) reduction in time to transport sample from the collection site to the NSO laboratory; (3) reduction of time required for confirmatory testing; and (4) submission of preliminary paperwork for provincial EAP approval while awaiting the results of the confirmatory genetic testing. Overall, Ontario NBS for SMA has successfully identified infants with SMA, enabling more timely access to treatment.

https://doi.org/10.1017/cjn.2021.231 Published online by Cambridge University Press

Table 1: Case summary and timing of screening results through treatment

	Case 1	Case 2	Case 3	Case 4	Case 5
Screening SMN1 copy number	0	0	0	0	0
Screening SMN2 copy number	3	4	2	3	3
			TIMELINE (Days of age)		
Baby born	0	0	0	0	0
Sample drawn	1	1	1	1	1
Sample received at NSO	3	6	3	4	3
Initial positive MassARRAY result obtained at NSO	8	13	5	6	8
Second tier MLPA result obtained at NSO	9	15	6	7	9
Referred to pediatric tertiary-care hospital	**10**	**15**	**6**	**7**	**9**
Parents contacted (retrieval)	10	15	6	7	9
Seen by neuromuscular specialist and Dx testing ordered	11	16	9	10	15
Confirmatory result obtained at clinical lab	12	24	13	14	18
Symptomatic on clinical exam at last visit before treatment?	No	Not applicable	No	Not applicable	No
First treatment	**24**	**Ongoing follow-up**	**18**	**Declined**	**32**

Acknowledgements

Biogen provided funding to Newborn Screening Ontario (NSO) for the pilot portion of this study.

Conflict of Interest

PC and AM were the recipients of a grant from Biogen which funded the first 6 months of SMA NBS in Ontario. AM has also been a consultant for Biogen and is a member of clinical trials for Biogen and Roche SMA studies. HM has received financial support for research endeavors from Roche and is on the advisory board for Novartis. All other authors have no declarations.

Statement of Authorship

KK and ML are responsible for laboratory supervision and reporting for SMA NBS. EY developed the assay and oversees regular performance. MK conducted data analysis for infants screened to date. HJM, CC, JJD, HG, MAT, JV, JM are involved in the retrieval and care for identified SMA infants. AM and PC lead implementation of SMA NBS, PC is Medical Director for NBS Ontario.

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https://doi.org/10.1017/cjn.2021.231 Published online by Cambridge University Press

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https://doi.org/10.1017/cjn.2021.231 Published online by Cambridge University Press