Screening for spinal muscular atrophy

Early diagnosis allows the possibility of starting treatment at a young age to achieve better outcomes

Rapid advances in technology and novel disease-modifying treatments will increase demands for early diagnosis and screening for many severe childhood conditions. This is exemplified by spinal muscular atrophy (SMA).

SMA is a rare but devastating autosomal recessive genetic neuromuscular disorder that results in significant disability and mortality. In its severest and most frequent form, SMA type 1, it causes progressive infantile paralysis, respiratory failure and premature death. The disorder results from insufficient levels of the survival motor neuron protein, caused by mutations in the survival motor neuron 1 gene (SMN1). The nearly identical survival motor neuron 2 gene (SMN2) produces a small amount of functional protein and modulates severity; SMN2 copy numbers in individuals range from zero to five (usually) and up to eight. Due to its rarity, with an incidence of about 1 per 11 000 births, and variable presentation, there is almost always a delay between symptom onset and diagnosis in these patients.

Research to date has employed several treatment modalities, including SMN1 functional gene addition, modulation of SMN2 to increase survival motor neuron protein production, neuroprotective agents, and targeted improvements of skeletal muscle strength and function. In early November 2017, nusinersen (an antisense oligonucleotide targeting SMN2), was registered as the first disease-modifying treatment for SMA by the Australian Therapeutic Goods Administration following results of pivotal studies in symptomatic infants and children with SMA. Nusinersen is administered intrathecally every 4 months after an initial loading period of four doses over 2 months. Potential adverse effects may include thrombocytopenia, proteinuria and vasculitis. As may be expected with a new therapy, the long term efficacy and safety are not yet determined. The underlying biology suggests treatment with nusinersen is non-curate in symptomatic patients and will be required lifelong. It would be naive not to anticipate ongoing significant morbidity lifelong despite the disease-modifying nature of this therapy. The nusinersen data have shown us that duration of symptoms inversely predicts response to treatment. In the NURTURE SMA study, pre-symptomatic infants with SMN1 mutations and two or three SMN2 copies (typically predicting a severe phenotype) were enrolled in an open label phase 2 study of intrathecal nusinersen. An interim analysis at one year showed that all enrolled infants were sitting, 64% who should be cruising were cruising, and 50% who should be walking were walking. This was a dramatic departure from the trajectory both of their older affected siblings and also of a cohort of symptomatic patients treated with nusinersen.

Now with an effective treatment, traction for newborn screening (NBS) for SMA is intensifying, and a solid case can be mounted that criteria from the World Health Organization Principles of early detection and more up to date criteria, including those from the Human Genetics Society of Australia (www.hgsa.org.au/documents/item/29), have been reached. NBS for SMA will enable the provision of a definitive diagnosis, avoiding the diagnostic delay following onset of symptoms that families commonly encounter. Natural history data suggest that the pre-symptomatic window may be brief (weeks or several months). Importantly, the benefit of early diagnosis and initiation of treatment on outcome is now recognised, with the most beneficial response to treatment to date seen in patients treated before the onset of symptoms. Given this timescale, NBS presents as the optimum and acceptable screening tool.

The public considers NBS for SMA to be of low risk and of potential benefit. There is no biochemical marker, but effective technology for primary DNA-based newborn bloodspot testing for SMA exists, using multiplex quantitative polymerase chain reaction, which is sensitive and specific. This technology, with a turnaround time of less than 3 days, has been implemented in many global NBS programs to identify severe combined immunodeficiency, including in most American states and, later in 2018, in New Zealand. This platform allows testing for multiple mutations with marginal time and cost increase. Pilot studies of SMA NBS have shown that cost may be reduced to less than $1 per specimen using the routine dried blood sample if multiplexed with severe combined immunodeficiency.

Of course there could be problems with NBS for SMA, including the pre-symptomatic identification of milder phenotypes and the psychological ramifications that may have on families. The current genotype—phenotype associations between SMN2 copy number and clinical severity will assist in selection of individuals who will have greatest benefit from early diagnosis, and it seems a test with very high sensitivity and specificity for the severe type 1 disease. Predicting age of onset in individuals with four or more copies of SMN2 is less certain, including the rare possibility of identifying a false positive result.
positive asymptomatic individual, adding complexity to predictive genetic testing. Clinical observation and commencement of treatment only following onset of symptoms in late-onset SMA (≥ 4 SMN2 copies) may offset these concerns, as disease progression is slow and is less likely to affect the outcomes.

There remain many unanswered questions regarding the new natural history of SMA in the era of disease-modifying therapy, including long term morbidity, impact of pre-symptomatic therapy in mild phenotypes, cost, and access to therapy. Despite these factors, there exists a moral obligation to support advances in NSW for SMA, with delays possibly threatening the integrity and equity of NSW and access to therapy. The Australian national policy framework for NSW is essential for consideration of which additional genetic conditions should be included in NSW and to develop protocols to manage the ethical issues, resource implications, referral pathways for positive tests and genetic counselling. The latter are likely to align with current NSW practice.

While NSW for SMA is sought, timely diagnosis of symptomatic patients is vital. Maternal child nurses, general practitioners and paediatricians are important in this process. The diagnosis should be considered in any infant presenting with severe hypotonia, poor head control and delayed motor milestones in the first year of life, with weakness and absent deep tendon reflexes prompting urgent referral to a paediatric neuromuscular clinic.

Pre-conception carrier screening (PCS) for SMA is also an important consideration. This screening is able to identify carrier status before having children and allows couples who are aware that they are at risk to select reproductive options to have healthy children. SMA has a carrier frequency of about one in 40. Pre-conception screening is generally favoured by the public and SMA families, with clinical utility and minimal psychosocial harm; however, concerns about carrier stigmatisation and social engineering have been raised. Commercial entities have recently offered PCS, but this is expensive and not widely accessed by Australians — examples include the prepair screen (www.vcgs.org.au/tests/prepair) for cystic fibrosis, SMA and fragile X syndrome, which costs around $300, and the Counsyl screen (www.counsyl.com) of about 120 conditions, which costs around $600. At present, pre-conception carrier screening is generally taken up in an ad hoc way, depending on whether women or their clinicians have heard about testing and whether they can afford it. Furthermore, 50% of pregnancies in Australia are unplanned. It is essential to have accurate and high quality educational resources to support pre-conception screening and also offer carrier screening in early pregnancy up to 12 weeks gestation. Advances in genetic technology have made PCS feasible for most autosomal recessive and X-linked disorders that have severe effects in childhood. Considerations for an expanded PCS program include the consensus in defining “severe” and the target population, reliability and accuracy of screening tests, components (i.e., equipment, education of the public and health care workers, data management, genetic counselling and follow-up interventions for carriers) and economic evaluations. In addition, there may be flow-on effects, with people at risk choosing expensive self-funded reproductive options.

The medical community should be aware of rapid changes in genetic technology and treatments in rare diseases. Pre-symptomatic diagnosis of early onset SMA provides the opportunity to initiate treatment to achieve optimal outcomes; however, genetic counselling and management of early identification of milder phenotypes are also important. The recent Australian national policy frameworks for NSW and population screening are ideally positioned to consider the complexities related to which additional genetic conditions should be included in screening programs.

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References are available online at www.mja.com.au.


