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Spinal Muscular Atrophy: A New Frontier but the Same Old Boundaries

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Spinal muscular atrophy (SMA) is a monogenic autosomal recessive disorder characterized by progressive and irreversible loss of anterior horn cells resulting in muscle wasting and weakness. SMA is a relatively rare disorder with an incidence of approximately one in 10,000 live births, yet it is also the leading genetic cause of death in infants worldwide.[1] Based on the number of live births in Ireland, this equates to between five and six new cases each year.

In recent years, novel disease-modifying treatments have dramatically altered the natural history of this condition.[2, 3] Treatment is most efficacious when initiated in the crucial pre-symptomatic phase, before irreversible motor neurone loss causes symptoms. Newborn screening (NBS) offers the single best opportunity to identify children early and pre-symptomatically.[4] Prior to the development of newer gene-based treatments, there was little to offer patients beyond the standard of care, based solely on symptom management and palliation. The arrival of newer disease modifying agents, spurred many groups internationally to develop clinical programmes for the administration of these novel agents. Given the clear benefit of pre-symptomatic treatment, many countries have developed newborn screening programmes in order to identify affected children in the first weeks of life.

At present, Ireland has yet to establish such a newborn screening programme and children here continue to present symptomatically. Clinical teams in Ireland have demonstrated their ability to initiate treatment rapidly and efficiently, following a confirmatory genetic diagnosis. Nevertheless, as current diagnosis depends on the detection of clinical signs and symptoms, symptomatic patients will invariably have a higher burden of disease than their counterparts detected through NBS programmes.

Testing in newborns involves a two-step genetic analysis of the dried blood spot (DBS) specimen collected for the routine newborn bloodspot-screening programme. Quantitative polymerase chain reaction (qPCR) is a commonly used technique for detecting the deletion of the survival motor neuron 1 (SMN1) gene.[5] A hypothetical screening pathway in this country would involve detection of a positive DBS screen. This would then result in a sequence of actions beginning with the newborn screening laboratory contacting the SMA treatment centre at Children's Health Ireland (CHI).

The treatment centre (CHI) would contact the parents of the screen positive child and offer an urgent face-to-face appointment. The family would meet with the neuromuscular specialist to discuss the screening results and the steps required to complete further diagnostic testing. Finally, the treating clinical team would definitively confirm the SMA diagnosis, and determine the SMN2 copy number via Multiplex ligation-dependent probe amplification (MLPA) analysis.[6] Genetic confirmation of SMA would clear the way for initiation of disease modifying treatment, which can be achieved shortly after genetic confirmation.

Currently in Ireland, two such treatments, Nusinersen and Onasemnogene abeparvovec (OA), are available. Risdiplam is approved by the European Medicines Agency (EMA), but not currently available in Ireland. The efficacy of Nusinersen treatment in pre-symptomatic infants continues to be examined through the single arm NURTURE study.[7] This study involves the treatment of 25 pre-symptomatic infants with SMA, who carry two or three SMN2 copies. In all patients, Nusinersen was initiated within the first 6 weeks of life. After a median of 2.9 years follow-up, all 25 children were alive and none required permanent ventilation. All could sit without support, 24 (96%) could walk with assistance and 22 (88%) could walk independently. In a pre-symptomatic cohort (n=14) treated with OA, the SPR1NT study reveals that all treated infants sat by 18 months of age, and 11 (79%) sat within the normal developmental window. Again, no children required respiratory or nutritional support.[8] An ongoing study investigating the use of Risdiplam in pre-symptomatic infants, RAINBOWFISH, indicates that based on preliminary results all children treated with Risdiplam (for at least a year) achieved independent sitting by 12 months.[9]

In cases where diagnosis and treatment are delayed, SMA patients must endure substantial and avoidable disability. [1] In the ENDEAR study, where symptomatic children (aged 7 months or younger) were treated with Nusinersen versus sham control, ventilator event free survival was only 61%, while less than 10% of children achieved independent sitting.[3] In the START trial investigating the use of OA in symptomatic children, three children were enrolled in a low-dose arm, the other 10 in a therapeutic dose arm. The patients in the therapeutic-dose cohort remained alive and without the need for permanent ventilation at 5-year follow up. While no patient treated with the therapeutic dose lost already acquired motor milestones, only two patients achieved a new milestone (standing with assistance), over the course of the study.[2]

A recent study in The Netherlands of the cost-effectiveness of NBS for SMA identified a lifetime saving of €12 million for patients identified and treated through NBS compared with patients identified through non-NBS treatment pathways.[10] In Europe, NBS for SMA is approved in the Netherlands, Poland, Slovenia, Germany, Belgium and Norway, while approximately 85% of newborns in the US are also screened. Given our current understanding, it is apparent that treatment response is time-critical, and the outcomes attainable for those in the pre-symptomatic versus symptomatic groups are starkly different. With this knowledge, we must ensure that we treat affected children with a clinical urgency that is reflective of the permanent and irreversible nature of disability resulting from unnecessary motor neuron loss. NBS presents the best and only route to ensuring access to treatment is timely, and maximally effective. In Ireland, the only remaining barrier to early diagnosis, pre-symptomatic treatment and better outcomes remains the lack of a dedicated SMA NBS programme.

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References:

1. Mercuri E, Pera MC, Scoto M, Finkel R, Muntoni F. Spinal muscular atrophy - insights and challenges in the treatment era. Nature reviews Neurology. 2020;16(12):706-15.
2. Mendell JR, Al-Zaidy SA, Lehman KJ, McColly M, Lowes LP, Alfano LN, et al. Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy. JAMA neurology. 2021;78(7):834-41.
3. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study. The Lancet Child & adolescent health. 2021;5(7):491-500.
4. Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genetics in medicine : official journal of the American College of Medical Genetics. 2020;22(3):557-65.
5. Vill K, Schwartz O, Blaschek A, Gläser D, Nennstiel U, Wirth B, et al. Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years. Orphanet journal of rare diseases. 2021;16(1):153.
6. Kariyawasam DST, D'Silva AM, Vetsch J, Wakefield CE, Wiley V, Farrar MA. "We needed this": perspectives of parents and healthcare professionals involved in a pilot newborn screening program for spinal muscular atrophy. EClinicalMedicine. 2021;33:100742.
7. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscular disorders : NMD. 2019;29(11):842-56.
8. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. Nature medicine. 2022;28(7):1381-9.
9. Finkel RS, Al-Muhaizea M, Farrar MA, Nelson L, Prufer A, Servais L, et al. RAINBOWFISH: A Study of Risdiplam in Newborns with Presymptomatic Spinal Muscular Atrophy (SMA) (4281). Neurology. 2021;96(15 Supplement):4281.
10. Velikanova R, van der Schans S, Bischof M, van Olden RW, Postma M, Boersma C. Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in The Netherlands. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2022.