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SPECIAL COMMENTARY

Pre-symptomatic spinal muscular atrophy: a proposed nosology

Finkel and Benatar highlight the ambiguity of the term 'pre-symptomatic' when characterizing infants at genetic risk for spinal muscular atrophy. They propose a conceptual framework that recognizes clinically silent and prodromal stages of pre-symptomatic disease and also accommodates emerging prognostic biomarkers.

With the expansion of newborn screening panels in many countries, more babies are being identified with serious genetic disorders and, hopefully, provided an opportunity for early treatment. Heterogeneity across these diseases, and indeed even within an individual disease, is such that the term 'pre-symptomatic' may be taken to mean different things. In some instances, this designation has created confusion and misunderstanding. It is, therefore, timely to reconsider the nomenclature for these individuals identified by newborn screening. The recent workshop report on amyotrophic lateral sclerosis (ALS) discussed the pre-symptomatic state for several genetic and idiopathic neurodegenerative diseases, and provides a useful context for considering a new nosology characterizing this phase of disease.[1] The example of spinal muscular atrophy (SMA) is used here to highlight these issues more specifically when considering patients identified by newborn screening, and a new tripartite classification is proposed.

SMA spans a broad spectrum of phenotypes, from infants with early-onset severe disease, to adult-onset indolent decline in motor function. SMA type 1 (SMA-1) is characterized by infants who appear clinically normal at birth but within the first weeks of life present with hypotonia, weakness, feeding and respiratory compromise, resulting in high morbidity, virtually no gains in motor development, and in the untreated state, death typically by 2 years of age.[2] SMA is caused by bi-allelic deletions or mutations in the *SMN1* gene. The number of copies of the 'backup' *SMN2* gene is a strongly prognostic modifier of disease: individuals with two copies have a 79% prediction of being type 1 and 16% the less severe type 2 form, while probabilities for those with three copies are 15% and 54%, respectively.[2]

Since 2016, three drugs for the treatment of SMA have been approved by regulatory agencies in multiple countries: nusinersen, onasemnogene abeparvovec, and risdiplam. Initial clinical trials and subsequent real-world experience have demonstrated that treatment of symptomatic infants with SMA-1 with each of these drugs improves motor function and prolongs survival, but the result is far from a cure.[2] Importantly, those babies treated sooner after symptom onset demonstrate a more pronounced response.[2] These observations led to the addition of SMA to newborn screening panels in several countries, with the expectation that identification of neonates in the window between birth and overt symptom onset would enable these drugs to be initiated in a 'pre-symptomatic' state and result in an optimal response. Clinical trials with these three drugs in infants diagnosed largely by newborn screening have demonstrated remarkable results, in many cases developing normally, without medical co-morbidities and with normal acquisition of motor skills at up to 5 years follow-up.[3–5] Nearly all of the infants with three copies of *SMN2* in these trials are demonstrating normal health and development. However, while trial participants with two copies of *SMN2* are generally doing very well, approximately one-third still show delays in the tempo of motor development, and some are having mild impairments in feeding and respiratory status.[3,4] The prospect for a cure in this population of patients is clearly much more muted. As such, it is important not to confuse 'pre-symptomatic' with an implicit expectation that treatment initiated at that time will result in a cure.

These observations question: (i) what exactly is meant by 'pre-symptomatic'; and (ii) whether there is a need to subcategorize 'pre-symptomatic' neonates who will progress to clinically manifest SMA. Relevant to the first question is whether these 'pre-symptomatic' neonates are entirely normal on neurological exam. The clinical trials evaluating the three drugs in 'pre-symptomatic' babies with SMA used broad inclusion criteria, allowing for investigator interpretation of whether incipient features of SMA such as mild hypotonia, weakness, and/or hyporeflexia were broadly within the range of normal.[3–5] Some of the participants in these studies had arguable but subtle features typical of SMA at screening, and in some cases even more evident at the time when treatment was initiated 1–3 weeks later. Moreover, the pool of motor neurons is reduced prior to symptom onset, with weakness only becoming apparent after motor neuron number has fallen below a critical threshold. Indeed, autopsy studies of infants with SMA have demonstrated that significant loss of motor neurons occurs in late foetal and early postnatal life, especially for individuals with only two copies of *SMN2*.[6] Parenthetically, autopsy studies of typically developing foetuses and infants show high levels of SMN protein in spinal cord tissue prenatally, a decline by 2.3-fold within 3 months after birth, and 6.5-fold decrease after 3 months of age.[7] Accordingly, there may be an optimal window of time following birth and before significant loss of motor neurons when these SMA drugs may restore survival motor neuron protein to remaining motor neurons. Initiation of treatment within this window, however, will not lead to recovery or regeneration of lost motor neurons to yield a pool of cells that is sufficient for normal motor development or maintenance of muscle function over time.[7] These 'pre-symptomatic' babies, with a reduced pool of motor neurons (which

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Table 1 Predictive biomarkers in spinal muscular atrophy

	SMN2 copy number	Ulnar nerve CMAP			pNF-H		
		n (reference)	Age, months	Amplitude, mV	*n* (reference)	Age, months	Concentration, pg/ml
Typically developing infants	N/A	27 (Kolb *et al.*[9])	3.3 (2.0)	5.5 (2.0)	6 (Darras *et al.*[11])	<1 year	1510 [579–7030]
		10 (Alves *et al.*[10])	1.9 (3.4)	12.0 (4.0)	10 (Alves *et al.*[10])	1.9 (3.4)	498 (261)
Pre-symptomatic infants	2	14 (De Vivo *et al.*[3])	0.6 (0.3)	2.7 (1.5)	13 (De Vivo *et al.*[3])	0.6 (0.3)	20 881 [845–52 900]
	3	10 (De Vivo *et al.*[3])	0.7 (0.3)	3.1 (1.1)	9 (De Vivo *et al.*[3])	0.7 (0.4)	1871 [959–7950]
Symptomatic infants	2–4	25 (Kolb *et al.*[9])	3.7 (1.7)	1.4 (2.2)	—	NP	NP
	2	15 (Kolb *et al.*[9])	<2 (NR)	0.5 (1.0)	—	NP	NP
	2	121 (Darras *et al.*[11])	5.6 (NR)	0.2 (0.2)	117 (Darras *et al.*[11])	5.6 [1.0–8.7]	15 400 [2390–50 100]

n = number of subjects reported; N/A = not applicable; NP = not performed; NR = not reported.
Compound motor action potential (CMAP) amplitude and plasma phosphorylated neurofilament heavy chain (pNF-H) levels at the initial evaluation of reported typically developing, pre-symptomatic and symptomatic young infants with SMA. Values are reported as mean (SD) or median [range]. Levels of pNF-H were measured using ProteinSimple® enzyme-linked lectin assay.

may be evidenced by relevant biomarker abnormalities), may appear normal initially but are at risk for developing muscle fatigue, weakness, and motor impairment later in life. Relevant insights may be gleaned from preclinical studies. For example, studies in the SMNΔ7 mouse model of SMA showed dramatic improvement in survival and motor function when animals are treated with an adeno-associated virus-mediated *SMN* gene transfer on postnatal Day 1 versus partial effect on Day 5 and little benefit on Day 10.[8]

Several informative prognostic biomarkers have been identified for SMA in addition to the *SMN2* copy number. Two others which have been utilized in clinical trials are discussed here. The compound motor action potential (CMAP) is an electrophysiological measure that quantifies the motor response following a supramaximal electrical stimulation of a peripheral nerve. The lower CMAP amplitude in SMA reflects a reduced number of motor neurons. CMAP data from typically developing, pre-symptomatic, and symptomatic infants evaluated in natural history studies are summarized in Table 1.[9–11] It is noteworthy that the eligibility criteria for enrollment in 'pre-symptomatic' clinical trials permitted babies to be enrolled whose CMAP was 1–2 SD below the mean for age-matched typically developing infants.[3–5] Data from one of these trials illustrate how pre-symptomatic babies with two or three copies of *SMN2* have mean CMAPs 1 SD below the mean for typically developing infants, indicating that as a group, there was already significant loss of motor neurons/functioning axons.[3] Second, measuring the neurofilament level in blood reflects the degree of ongoing axonal degeneration.[11] Plasma levels of phosphorylated neurofilament heavy chain (pNF-H) have been studied in symptomatic SMA-1 patients,[11] and were examined in one 'pre-symptomatic' drug study[3] and one retrospective cohort study,[10] as summarized in Table 1. The pNF-H level in a small number of typically developing infants was approximately one-tenth that seen in symptomatic SMA-1 infants with two copies of *SMN2*. Pre-symptomatic babies with two copies of *SMN2* in one study had levels even higher than the slightly older symptomatic babies.[3] While pNF-H levels are mildly elevated after birth in typically developing infants, and decline over time, presumably as axons are pruned, the 10–13-fold increased levels in both the 'pre-symptomatic' and symptomatic infants are striking. Thus, the CMAP and neurofilament levels can serve potentially as prognostic biomarkers, even when the patient appears normal on exam. The sensitivity and reproducibility of a biomarker assay or clinical test is important to consider here. Other prognostic biomarkers will certainly be identified in the future.

How then should this population of genetically defined individuals with SMA be characterized properly? Consistent with the nosology for ALS proposed by Benatar *et al.*,[1] we envision three phases of SMA based on clinical symptoms and signs, with the emergence of biomarker abnormalities grafted onto this conceptual framework (Fig. 1).

(i) 'Clinically silent (pre-manifest) disease' describes individuals with bi-allelic *SMN1* deletions/mutations who appear clinically normal. The parents report no symptoms, and an experienced paediatric neurologist regards the motor examination as normal.
(ii) 'Prodromal disease' encompasses those individuals who have subtle symptoms and/or findings on examination that are consistent with SMA but are not definitive. The terms 'pauci-symptomatic' and 'oligo-symptomatic' have sometimes been used to describe these patients.
(iii) 'Symptomatic SMA' is the term reserved for those individuals with definite clinical findings that are typical of SMA.

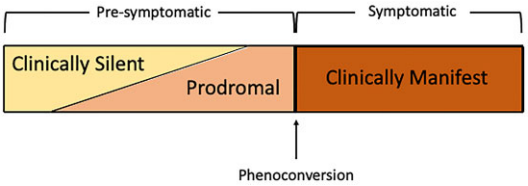

Figure 1 Proposed nosology for classification of infants with SMA identified by newborn screening. Spinal muscular atrophy (SMA), as a biological entity, is understood to comprise three phases. First, a clinically silent phase in which individuals with bi-allelic *SMN1* mutations/deletions appear clinically normal. Second, a prodromal phase during which subtle symptoms or findings on examination emerge. Finally, a clinically manifest stage, which represents the clinical syndrome that is recognizable to the experienced clinician. The clinically silent and prodromal stages are considered 'pre-symptomatic', while the clinically manifest stage is considered 'symptomatic'. The term 'phenoconversion' describes the transition from pre-symptomatic to symptomatic stages of disease. While we recognize that this process may be gradual, there is value in an operational definition that clearly differentiates this transition. Moreover, akin to that proposed for ALS, we use the term 'phenotransition' to describe the transition from the clinically silent to the prodromal stage of disease. As described in the text, biomarker abnormalities may be apparent during each of these stages of disease, with *SMN2* copy number, CMAP amplitude and serum pNF-H levels prognostic of the occurrence and timing of phenoconversion.

There are several reasons for our recommending against incorporation of known biomarkers—CMAP amplitude, plasma pNF-H and *SMN2* copy number—into the definition of each phase of disease. First, there is something intuitive in defining these phases of disease based on clinical phenomenology. Second, some (i.e. *SMN2* copy number) are static irrespective of the clinical evolution of disease. Third, the technology for quantifying some of these biomarkers (e.g. pNF-H) is still evolving; and age-appropriate normative data are not well-established (e.g. pNF-H and CMAP). Finally, new biomarkers are likely to emerge, and these are likely to complicate operationalization of the proposed tripartite classification if it only incorporates currently available biomarkers. Nevertheless, we recognize that each of the currently available biomarkers has prognostic value—with lower CMAP amplitude, higher plasma pNF-H and lower *SMN2* copy number predicting earlier emergence of symptomatic SMA. As such, we recommend that individuals categorized according to our proposed tripartite clinical classification, also be characterized with respect to known biomarkers. Such a parallel approach could serve the clinical need of aiding the clinician in framing the discussion with parents and presenting reasonable expectations when initiating treatment for their baby; and the research needed to better understand expected trajectories of disease in response to an intervention. The lessons learned from SMA may apply broadly to other diseases identified by newborn screening.

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Competing interests

R.S.F. has participated as a principal investigator in clinical trials of nusinersen (Biogen), onasemnogene abeparvovec (AveXis/Novartis) and risdiplam (Roche) in presymptomatic infants with SMA and has served as a paid advisor to AveXis, Biogen, Genentech, Novartis, Roche and Scholar Rock; he receives licensing fees for the co-development of the CHOP INTEND motor function scale for SMA. M.B. has participated as a principal investigator in ALS clinical trials funded by Orhazyme and Biogen. He has also served as a paid advisor to Biogen, Denali, Roche, Alector and Novartis. In addition, M.B. has a provisional patent entitled 'Determining Onset of Amyotrophic Lateral Sclerosis'.

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