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285th ENMC international workshop: SMN-associated neurodevelopmental disorder: type 1 spinal muscular atrophy and the brain, 31st January - 2nd February 2025, Hoofddorp, The Netherlands

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ABSTRACT

Recent advances in spinal muscular atrophy (SMA) early diagnosis and treatment have significantly improved survival and motor outcomes, particularly for those with severe phenotypes. However, clinicians have observed unexpected cognitive, social, communication, and behavioural differences in a proportion of children. The 285th ENMC workshop convened 28 experts from 13 countries to address these neurodevelopmental concerns. Key outcomes included confirming the presence of challenges in neurodevelopment in a substantial proportion of treated SMA type 1 children, identifying higher-risk subgroups, and emphasizing the need for early identification, timely referrals, and family support. Participants agreed on a core screening strategy and highlighted the importance of international collaboration to develop specific diagnostic and intervention guidelines. Future steps involve launching an online survey to assess the prevalence of neurodevelopmental disorders and study their characteristics and trajectories, developing care guidelines, and promoting research working groups to further understand brain development in SMA and improve patient care.

1. Introduction and background

The 285th ENMC workshop on "SMN-associated neurodevelopmental disorder: type 1 spinal muscular atrophy and the brain", was held from 31st January to 2nd February 2025. It brought together 28 participants, including paediatric and adult neuromuscular and central nervous system (CNS) clinical experts, child psychiatrists and psychologists, neurobiologists, and advocacy group representatives with lived experience.

Spinal muscular atrophy (SMA) is a recessive neuromuscular disorder characterized by progressive muscle atrophy and weakness, variably affecting motor, respiratory and swallowing function. SMA is caused by deletions or pathogenic variants in the survival motor neuron 1 gene (SMN1), which leads to the degeneration of motor neurons in the spinal cord [1]. The disease presents a wide range of phenotypes, that are historically classified into clinical groups on the basis of onset age and maximum motor milestone achieved: severe prenatal/congenital form, with reduced foetal movements, congenital contractures, and early respiratory failure (type 0), very weak infants unable to sit unsupported (type 1), non- ambulant children able to sit independently (type 2), and ambulant individuals with childhood (type 3) and adult onset SMA (type 4) [2]. SMN2 is a paralogous gene, considered a phenotypic modifier, and most transcripts encode a less stable form of the SMN protein. Multiple copies of SMN2 are associated with milder phenotypes, contrasting with the most frequent genotype of two SMN2 copies and SMA

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type 1 [3].

The recent availability of innovative therapies, specifically SMN2 splicing modifiers and gene replacement therapy, have dramatically changed survival, the natural history and clinical outcomes, in particular for children with, or genetically predisposed to, SMA type 1 [4–11]. As a result, the increasing number of long-term SMA survivors has revealed emerging phenotypes, including notable changes in motor function and other areas of development, such as cognition, language and social skills.

One therapeutic situation is that of children initiating disease modifying therapy before the disease is clinically manifest (presymptomatic stage), whether diagnosed through newborn screening (NBS) or due to a family history of SMA. In this context, motor prognosis has shown to be excellent, with children demonstrating the acquisition of motor milestones such as sitting and walking independently. For some, timeframes may be comparable with typically developing children. This suggests that these therapies are most effective when administered before any signs of motor neuron degeneration appear [12]. Alternatively, children can initiate treatment following symptom onset and clinical referral. This latter paradigm accounts for most treated children, particularly those with the longest treatment duration and in regions without NBS for SMA. Follow-up of this population has progressively questioned the occurrence of differences in cognitive or social skills, delay in communication abilities, and behavioural challenges in some children [13–17].

Currently, there is limited understanding of how frequently these differences occur, when they start to appear and when we can reliably detect them, which areas of development are most impacted and how these change across the lifespan of the individual, what underlying factors contribute the heterogeneity of outcomes, and whether emerging SMA treatments influence their presence and severity

The aim of this workshop was to bring together experts, including clinicians, scientists, researchers, and advocacy representatives, to discuss neurodevelopment in children with SMA, particularly in the most severe phenotype (type 1) and in those diagnosed through NBS or prenatal testing. A key focus was addressing parents' concerns by considering neurodevelopmental assessments to aid early detection of developmental differences. Additionally, the workshop aimed to identify knowledge gaps, set plans for future research in SMA to understand the neurobiology, improve epidemiology and diagnostic tools, and provide care guidelines and evidence for potential treatments, to optimise neurodevelopmental outcomes for affected children.

2. Neurodevelopment in SMA across the lifespan: experiences in different regions of the world

David Gómez-Andrés shared the findings of a pre-workshop survey conducted to gather clinical experiences and professional perspectives among all workshop participants. Professionals from 16 expert centres across Europe, North America and Australia responded to the pre-workshop survey via Redcap. Most clinicians had more than a decade of experience in both neuromuscular and neurodevelopmental care, worked in public health systems and had access to all three approved SMN-restoring therapies. Survey responses delineated a consistent, yet still incomplete, picture of neurodevelopmental morbidity.

All centres managing individuals with SMA type 1 reported language delay, social-communication deficits or broader cognitive impairment in these children. The median proportion of affected individuals was approximately one-third, although individual estimates ranged from 10 % to >70 %. Neurodevelopmental complications were less frequently reported in those with SMA type 2, and sporadically noted in children with SMA type 3. Neurodevelopmental challenges were also apparent in infants treated whilst presymptomatic—particularly those harbouring two SMN2 copies—indicating that early pharmacological intervention does not fully prevent the risk of neurodevelopmental differences.

Clinicians converged on delayed expressive speech as the most pervasive phenotype. Receptive language appeared relatively preserved, whereas deficits in social interaction, the presence of restricted interests and, less frequently, executive dysfunction were also reported. Approximately half of respondents perceived that these phenotypes showed improvement over time. Potential modifiers extended beyond canonical disease factors—SMN2 copy number and gross-motor status—to environmental influences such as prolonged hospitalisation, excessive screen exposure and socio-economic context.

Assessment practices were notably diverse. Audiological evaluations were usually normal, and brain MRI or extended genetic testing was reserved for individuals with additional specific red flags. No single cognitive or behavioural battery emerged as a reference standard; each centre employed its own instrument panel, and many clinicians cited logistical barriers—time constraints, motor fatigue, personal protective equipment (e.g. face masks) and limited attention span—that complicate formal testing. Disparities in experience with presymptomatic cases revealed uneven implementation of NBS in different countries with SMA NBS operational in nine of the 16 participant centres. The international survey identified the unmet need for SMA-specific cognitive and behavioural test batteries, capable of refining prevalence estimates, characterising the natural history of neurodevelopmental manifestations, and identifying modifiable risk determinants as part of multicentre studies.

Subsequently, clinicians from 10 countries shared historical and current data including The current experiences were presented by experts from reference centres in countries from Europe (Belgium, France, Italy, Turkey, Spain, UK) North and South America (US, Chile), and Australia (see list of participants). An overview of the previous published studies discussed is summarised in Table 1 and outcomes from the specific centres denoted in supplementary Table 1. Many clinicians reported that different neurodevelopmental profiles were apparent among specific patient groups, using a framework that incorporated the modality of diagnosis (newborn screening vs. clinical diagnosis), the clinical status at the time of diagnosis (clinically manifest or silent), and the number of SMN2 copies.

There was agreement that for treated children with SMA type 1 (or at risk of SMA type 1 due to genotype of 2 SMN2 copies), frequent signs of neurodevelopmental vulnerability were observed, and an expanded phenotype was apparent. Difficulties or delays in several domains were reported, including speech articulation, expressive language, and social communication. Global delay, restricted interests or repetitive behaviours recalling autism spectrum disorders, atypical behavioural patterns, reduced attention, and/or hyperactivity were also observed. In individual cases, epileptic seizures were noted. Since children with SMA type 1 or with 2 SMN2 copies are also more likely to manifest more marked bulbar, respiratory and motor impairments, caution regarding pathogenesis was acknowledged due to the presence of these because there are many potential confounding variables. Even so, for children with 2 SMN2 copies, initiating treatment whilst presymptomatic and little or no motor impairment on follow up, there may be also be unexpected neurodevelopmental difficulties, such as isolated expressive language delays, verbal dyspraxia, and stuttering. The common pathogenesis was hypothesised to be a consequence of the pathogenic impact of SMN deficiency during the prenatal period and in early life in the developing brain, mediated by the number of SMN2 copies. The type of SMN restoring therapy seemed not to have an impact in the occurrence of neurodevelopmental abnormalities.

While the data presented was not always supported by standardized assessments, all experts agreed that currently available tools for assessing neurodevelopment in children with SMA were not adapted, in particular for the symptomatic population with significant motor and/or bulbar-respiratory weakness. Therefore, developmental pediatricians commented that the cognitive and behavioral phenotypes in SMA were yet to be fully characterized by systematic clinical and neuropsychological studies, to allow for systematic categorical diagnoses of these possible SMN-associated neurodevelopmental disorders (SANDs). The

Table 1
Previously published studies on neurodevelopmental outcomes in children with SMA.

Author/date/Region	Study Design and measures	Sample demographics and clinical characteristics	Results
2002, Rivière, France [18]	Case control, memory-for-locations task	12 SMA2, mean age 30 months, untreated	Locomotor impairment not a key risk factor for slowing acquisition of spatial search skills
Mennetrey 2020, Necker, France [19]	Cross-sectional cohort	17 SMA2, untreated and 60 normal control children	Similar mean IQ, and cognitive flexibility in SMA 2 and controls. SMA 2 showed fragility in verbal memory with possibility of late onset attention difficulties.
2024, Steffens, Johannsen, Germany [20]	Cross-sectional cohort, <4 yrs: BSID-III ≥5yr: WPPSI-IV	19 SMA1 (≤3 *SMN2)* 1 presymptomatic, treated	11/19 (55 %) demonstrated subnormal cognitive development. Risk factors for cognitive impairment included male sex and the need for ventilatory or feeding support.
2024, Kolbel, Germany [14]	Cross sectional cohort, BSID-III	40 NBS cases (34 presymptomatic), treated 17 2 SMN2 11 3SMN2 12 ≥ 4 SMN2 (age 23–42 months).	Cognition: 14/40 below avg (10/14 = 2*SMN2)* Motor: 14/25 below avg (9/14 = 2*SMN2*), Receptive language: 12/33 below avg (2*SMN2* evenly distributed). Expressive language: 11/34 below avg (2*SMN2* evenly distributed). Cognitive development in SMA patients identified through NBS appeared to be influenced by number of *SMN2* copies.
Tosi, 2023, Italy [15]	Cross sectional cohort, Griffiths III, VABS-II	15 SMA1 treated	Global developmental delay in majority (mostly due to gross motor function) Normal scores in learning and comprehension of language. Difficulties in expressive language (not only due to phonetic-phonological disorders.
Buchignani, 2024 Italy [21]	Multicentre, cross-sectional and longitudinal study, MB-CDI	24 SMA1 and 12 diagnosed through NBS, treated	Comprehension preserved; Gesture development <5th percentile in most SMA1 (none of NBS) Lexical expression < 5th percentile in most SMA1, 50 % NBS. (iimprovements observed at follow-up in both groups)
Bitetti, 2024, Italy [22]	Longitudinal, Griffiths III	12 SMA1 treated	At 12 months, improvements in cognitive and communication skills, however most scores remained <70, indicating an overall developmental delay

Legend: BSID-III, Bayley's Scales of Infant Development – third edition; MB-CDI, MacArthur-Bates Communicative Development Inventory MB-CDI; SCQ, Social Communication Questionnaire; WPPSI-IV, Wechsler Preschool and Primary Scale of Intelligence- fourth edition; VABS-II, Vineland Adaptive Behavior Scales – Second Edition.

group highlighted the feasibility and importance of incorporating adapted tools for the early detection of communication and behavioural difficulties in children with SMA type 1 and the importance of acquiring data in children initiating treatment while presymptomatic (with less confounding motor and bulbar symptoms). In the context of a disease that continues to evolve due to advances in therapy, the group concluded that the results supported the need for increased clinical attention to neurodevelopmental aspects. Important knowledge gaps appeared on several fronts: which therapeutic modality—or combination—offers the best risk-benefit balance; the exact window in which treatment should begin; and which standardized, validated measures could reliably capture efficacy. Because outcome tools are heterogeneous, it remains unclear whether neonatal intervention alone safeguards typical development, or if additional biomarkers are needed to detect residual neurodevelopmental risk. In addition, neurodevelopmental outcomes with prenatal/in-utero treatment should be explored.

On the other end of the age spectrum, Magda Mroczek highlighted the imperative for medical and educational communities to be able to address the emerging needs of an aging population of individuals living with SMA type 1. Several studies have examined cognitive functioning in older children, adolescents and adults, with findings ranging from individuals with normal intelligence and preserved language comprehension to cognitive impairments [23,24]. However, data gaps include lack of evidence on school performance concomitant with limited information regarding behavioural concerns in this population, including symptoms suggestive of attention-deficit/hyperactivity disorder (ADHD) or behaviours associated with autism spectrum disorder (ASD). Nevertheless, findings from a small case series suggest that ASD-like features may be more prevalent in this cohort than previously recognized. In a Polish cohort of children with SMA type 1, parents described behavioural irregularities in some treated children. These included signs of motor hyperactivity, difficulty in forming close peer relationships, oppositional or inappropriate behaviour, and challenges with sustained attention in children aged 5 to 8 years [25]. It is important to consider that such behavioural characteristics may not be always intrinsic to SMA1 itself and hereditary factors (e.g., a family history of ADHD, as observed in one case) or early-life environmental variables should be considered. Magda Mroczek recalled that a number of interventions and programs developed for adults and older children with neuromuscular or other chronic conditions leading to motor, respiratory, bulbar or neurocognitive disability could be used if adapted to the needs of people with SMA type 1. These may be particularly valuable in addressing issues such as reduced facial expressiveness, academic performance difficulties, and broader psychosocial challenges. Promoting psychosocial well-being in this context involves fostering a sense of meaningful participation, supporting core psychological needs such as autonomy and social. connectedness, and encouraging engagement with patient advocacy and support organizations. In addition, caregiver burden must be routinely monitored through informal yet consistent assessments and mitigated where possible. Peer-led support groups have shown promise in reducing stress and improving emotional resilience among caregivers and may offer an effective means of support.

Renske Wadman explored the assessment of bulbar function in SMA type 1 and its impact on in socio-cognitive problems. Impairment of bulbar function is present in a substantial proportion of these children, in particular those with 2 SMN2 copies, affecting swallowing, facial expression and articulation. Articulation issues can also lead to speech delay or impairment, and impact social interaction. This can complicate the assessment of speech and language. Prior to the availability of SMN restoring therapies, early case series reported notable impairments in speech development [26–28], with up to 38 % of children with SMA type 1 unable to communicate or only vocalize. Confounding factors, such as frequent hospitalizations, medicalization (frequent aspirations), acute hypoxia, chronic hypoventilation, and ventilatory support (>16 h/d), may limit insights into pathogenesis. Most children who developed comprehensible speech were less severely affected and able to hold their head upright (onset 3–6 months, SMA type 1c), however speech difficulties were evident and included weak voice (27 %), need to repeat sentences frequently (46 %) and altered facial expression [29]. There is limited data on whether SMN restoring therapies affect speech development. Two case series reported that the majority of children with SMA

type 1 (n = 24) treated with onasemnogene abeparvovec developed speech [22,30]. Due to the presence of neuromuscular junction disturbances in SMA, pyridostigmine has been proposed to ameliorate bulbar weakness and improve symptoms of bulbar dysfunction and speech in children and adults with SMA types 2 and 3 children and adults [31] although some experts recommend for cautious use due to problems derived from increased production of saliva.

As a conclusion, experts agreed that assessment of speech delay in treated SMA type 1 children is challenging, particularly for those with bulbar dysfunction or severe motor weakness. In any SMA type 1 individual, assessment of mouth opening, facial and tongue movements, swallowing, sounds articulation and cognitive function should be undertaken, ideally by experienced teams [23]. In the absence of adapted tests, there is an urgent need to develop SMA specific scales to assess speech and to investigate speech development in children with SMA type 1 receiving SMN restoring treatments.

3. Patients' perspective

Portia Thorman shared her personal insights as a mother of a child affected by SMA type 1, along with her experiences supporting the UK SMA community. Since NBS is not available in the UK, observations came from symptomatically treated patients, whose early experiences are shaped by their health. She highlighted key caregiving factors affecting neurodevelopment in children with SMA, including limited environmental exploration, prolonged hospital stays, social isolation induced by parental fear, speech difficulties requiring constant interpretation, lack of social mealtimes, and reliance on digital devices for play, among others. To promote optimal neurodevelopment in children with SMA, families urge early multidisciplinary interventions across multiple domains. These include: motor interventions, such as early introduction of electric wheelchairs and ensuring correct posture; bulbar interventions for language, feeding, and secretion management, with ongoing monitoring of the effectiveness of these therapies; and social interventions, including early social skills groups, accessible toys, and optimized use of electronic devices. Educating parents on recognizing early signs of developmental difficulties and increasing awareness of these challenges among healthcare professionals is also crucial to ensuring better support for families affected by SMA. Families also emphasize the importance of peer support groups for parental mental health, which has a direct impact on child development.

Yasemin Erbas highlighted several underexplored neurological topics in SMA, such as seizures and brain pathology, which so far have not received much attention, despite their potential impact on cognitive function. She noted that currently available assessment tools for neurocognitive function are not validated for children with neuromuscular diseases. This raises several concerns: physical disabilities may affect results (e.g., bulbar issues leading to underestimation), SMA-specific symptoms may differ from those in non-SMA children, and these symptoms might go unnoticed unless specifically assessed using appropriate tools. Early intervention strategies, such as speech therapy, are commonly recommended, however, there is limited evidence on the effectiveness of standard therapies in improving outcomes for SMA patients. Moreover, neurocognitive functions develop during critical normative or sensitive periods, making timely intervention crucial.

4. Factors influencing SMN-associated neurodevelopmental disorders

Michelle Farrar introduced the discussion on factors influencing the SANDs by presenting an overview on known SMA genetic modifiers. SMN2 copy number variation is a critical modifier, with more copies associated with milder neuromuscular phenotypes. Data from experts' experiences and a few published studies support the role of SMN2 copy number in socio-cognitive phenotypes. Other variants that modify neuromuscular phenotypes by acting on SMN expression may also be relevant to SMA neurodevelopmental phenotypes, such as rare SMN2 polymorphisms (c.859 G>C and c.835-44A>G). Precise SMN locus genotyping will be necessary to further understand SMN associated neurodevelopmental disorders [32]. Whether there is a functional role of NAIP in SMN neurodevelopmental disorders may also be considered by mapping the deletion boundaries at the SMN locus. While SMN protein levels, functions, and interactions within molecular and neural networks in the developing brain are a critical focus, various open questions regarding additional potential genetic modifiers were posed: i) The role of non SMN variants that modify the neuromuscular phenotype such as plastin 3, an actin binding protein, and neurocalcin-δ, a calcium binding protein. Their roles in cytoskeletal dynamics and signalling may play a role in neuronal development and maturation [33], ii) Studies in neurodevelopmental disorders provide evidence for gene-environment interactions, with exposure to early life adversity events modifying brain structure and function and affecting neurodevelopment, mainly through epigenetic mechanisms. Prenatal factors (e.g. poor foetal growth, substance use, maternal anxiety or depression), and intrapartum or postpartum factors (e.g. low socioeconomic status, maternal depression) can result in changes in DNA methylation, histone modifications, and chromatin remodelling and change gene expression without altering DNA sequences [34]. Therefore, collecting data on environmental risk factors (inflammatory, metabolic and psychosocial) should be included as part of comprehensive phenotyping in SMA, especially considering that exposure to environmental enrichment and positive influences may revert these effects.

Peter Claus presented his group's work on the SMN interactome showing how it could play a role in understanding the SANDs. Their work is based on previous studies on the SMN-irreversible degenerative processes which must be considered in patients who experience delays in starting treatment with disease-modifying therapies and in non-responders [35]. It is unclear which pathological changes underlie this SMN-irreversibility however, they become manifest in altered signalling modules as described by molecular systems biology. During disease progression, a reduced regenerative capacity is observed, and it is reflected by a growing network of dysregulated signalling nodes, with an increased fraction of SMN-irreversible versus SMN-reversible signalling mediators. Claus and colleagues hypothesised that highly connected SMN-irreversible nodes may be potent new treatment targets, with the RhoA kinase (ROCK) and the ERK pathways being promising candidates based on a priori network analysis. Professor Claus showed their procedure of SMN "proxisome" analysis, which enabled them to show the interaction of SMN with many proteins, including enzymes involved in metabolic processes. He also presented a multicentre international effort to analyse the systemic characteristics of SMA using proteomics, phosphoproteomics, translatomics, and interactomics from two SMA mouse models (Taiwanese and Smn2B/-) [36]. It was explained how linking a disease-causing molecule with widespread molecular dysregulations via multiomics represents a paradigm for elucidating relevant regulators of molecular pathomechanisms in monogenic diseases. Based on this, an active study is evaluating dysregulated transcripts in the hippocampus and frontal cortex in a severe SMA mouse model (Taiwanese).

Nicola Molitierno presented his group's work on brain organoids and how they can provide insight on brain involvement in SMA [37–40]. They generated spinal cord and brain organoids from both healthy individuals and people with SMA type 1. SMA brain organoids displayed developmental defects and altered electrical activity similar to but independent of observations in spinal cord organoids. Treatment with novel r6-MO modified antisense oligonucleotide significantly increased SMN protein levels and rescued neural differentiation, reduced apoptosis, and improved functional activity in SMA organoids [41]. Their findings show the occurrence of early neurodevelopmental defects in SMA and suggest that early intervention with optimized ASO therapy could modify pathology. Stem cell-based models, including spinal and brain organoids, could therefore provide valuable insights into the mechanisms underlying SMA and brain involvement, and the

integration of advanced 3D models with in vivo studies will be essential for developing more effective, early-stage treatments for SMA.

Thomas Crawford discussed the neurobiology of SMA, drawing attention to the paradox that SMN augmenting therapies are initiated at a time of the normal perinatal decrease in SMN protein levels. It is during this period that neurons are highly susceptible to undergo programmed cell death and the time that connections are being made with other cells. Several hypotheses for these observations were proposed: i) different developmental processes, or ontogenic capabilities, ii) ongoing maintenance and expression requirements, iii) downstream factors. Possible mechanisms to guide research and model the impact of deficient SMN in the brain also include: i) a fixed pathology early in genesis that is unveiled by development, ii) a disorder of the process of development itself, and iii) a degenerative disorder that occurs during development and may continue after development concludes. Clinical observations such as walking deficits not commensurate with power, raise further questions about CNS pathology in SMA, noting previous pathological findings in Clarke's column and the cerebellum [42].

Tom Gillingwater presented published and unpublished data from a range of mouse models of SMA that provide evidence for the contribution of the SMN protein in the brain, in both pre-natal and post-natal pathologies [43,44]. There are prenatal disruptions in cell proliferation particularly affecting brain regions such as the hippocampus in mouse models of the severest forms of SMA, and there are significant disruptions to the proteome of the pre-natal brain in SMA mice, indicative of more fundamental perturbations to normal developmental pathways. Insights into the latter are provided by translatome profiling, revealing a role for SMN protein in ribosome biology [45], incorporating a primary ciliopathy [46]. The latter can be corrected with SMN augmenting therapies yet highlights the importance of early treatment to a developing nervous system. It was noted that there is currently a lack of experimental data from mouse models of milder forms of SMA, as well as a lack of data informing on the potential impact of SMN-restoring therapeutic interventions on these developmental phenotypes. More research is therefore urgently required to understand the fundamental biology underlying the role(s) of SMN in brain development in vivo.

5. The role of biomarkers

David Germanaud discussed the current state of neuroradiological techniques as a potential biomarker in people with SMA. He acknowledged that understanding the cognitive and behavioural phenotype in SMA, particularly under early-start disease modifying therapy, is definitely needed at this stage, and will require scaled-enough prospective clinical and neuropsychological studies, likely to involve several neurodevelopmental diagnostic categories as an outcome. He differentiated the approach in two subsets of populations, those initiating treatment after symptom onset and with minimal clinical manifestations, or presymptomatic.

Severe motor impairment could be a driver or at least modifier for neurodevelopmental problems and both neurodevelopmental diagnosis and understanding the pathogenesis will be complicated due to the many confounding variables.

Meanwhile, knowledge of the brain's structural phenotype in SMA, especially in early-treated type 1, is still rudimentary even though it could be a decisive intermediate or complementary feature. Most publications rely on conventional radiology: scans look normal at birth but show diffuse atrophy later, observations drawn mainly from severely affected cases and therefore prone to reporting bias [47]. A recent case–control series of treated patients found an excess of MRI abnormalities—chiefly ventriculomegaly and enlarged subarachnoid spaces—but no link to SMN2 copy number, SMA subtype, or motor status was found; statistical power, however, was limited [48]. The only computational MRI study to date, confined to individuals with SMA types 3 and 4, suggested subtle cortical and cerebellar alterations [10]. Routine imaging is usually performed only when clinical progress falters, hampering retrospective efforts to define a neuroanatomical signature in early-treated SMA type 1. Although MRI is not required to diagnose SMA-related cognitive disorders, it can aid differential diagnosis and illuminate pathogenesis. Prospective, quantitative MRI acquired at birth and during follow-up could reveal global or region-specific anomalies in volume, maturation, and connectivity in infants with two SMN2 copies, or uncover atypical post-treatment developmental trajectories. Such a strategy is technically feasible and already undertaken in other high-risk neonatal groups, including extremely pre-term infants and those exposed to prenatal alcohol. A proposal for integrating standardized, computational brain imaging into research cohorts receiving early therapy for SMA (e.g. in a number of expert centers) could help to understand the role of neuroimaging in children with SMA type 1 and investigate the more impacted anatomic regions.

David Gómez-Andrés reviewed a spectrum of other emerging biomarkers that could sharpen the characterization of cognitive function in SMA. Genetically, SMN deficiency acts as a high-risk allele for neurodevelopmental disorders and additional modifiers—such as recessive variants seen in consanguineous families or other rare genetic variants—likely explain much of the cognitive heterogeneity [49]. Confirming their role will demand far larger cohorts, which makes further research on the topic difficult. Behaviorally, eye-tracking paradigms using Tobii® eye-tracking already provide motor-independent measures, with studies in Belgium, Japan and Brazil [50,51]. These tools show promising capacity to probe cognitive and executive skills and their translation to ecological paradigms could give insight in everyday attention and early deviations from typical development. Complementary digital tools—video-derived movement metrics, facial-expression and speech analytics, sleep-quality monitors, and geolocation traces—offer continuous, ecologically valid windows on cognition and environment, including screen exposure and parenting style. Finally, soluble markers familiar from ASD and ADHD research (single molecules such as oxytocin or GABA and broader metabolomic, proteomic and microbiome profiles) could add physiological depth to behavioral data [52,53]. The challenge is integration: without standardized protocols and multimodal frameworks these diverse signals cannot yet yield a coherent cognitive phenotype or guide personalized care in SMA cognition.

6. What we can do?

6.1. Early intervention in neurodevelopmental disorders

Lisa Ouss (neuropsychiatrist) discussed the necessity of early (clinical) screening tools and interventions for proposed neurodevelopmental disorders associated with SMA, to guide early diagnosis and interventions. She described the expanding knowledge on the aetiology of autism spectrum disorders (ASD), noting an increasing number of genetic conditions associated with syndromic autism and intellectual disability [54]. She described the experiences to be gained from understanding the early signs and interventions used in children with ASD, leveraging this experience for children with SMA [55]. Conversely, she raised the potential for SMA to generate new knowledge on the early psychopathological processes in neurodevelopment disorders. The evidence for an autistic prodrome would imply a specific temperament profile with passivity and perceptive sensitivity. Subtle differences in general attention and attention to social stimuli would be noted as domains where early signs could present [56–58], with further non-specific development delays in motor and social behaviour considered 'at risk' signs in the first six months of life [59,60]. A study was presented that detailed clinical signs gleaned of mother-child interactions and early symptoms from home movies that could be used as early screening tools for children with autism, as early as four months [61]. A paucity of anticipatory posturing when stimulated (e.g. by tickling) is currently considered a key early feature for children with autism. There is an emerging knowledge of the natural history of ASD,

being considered that the presence of autistic traits, and deterioration in the duration of eye contact may be noted as early as 2–6 months of age [62]. Clinical experience and recent studies show that children with early and late onset autism could gain expressive and receptive language skills, in parallel with a neurotypical peer group. Shared positive affect may improve till 18 months. It may decline thereafter in children with early ASD and show a progressively deteriorating course in children with later onset ASD. Whilst the skills of initiation of joint attention accrued in neurotypical peers, children with early and late onset ASD persisted with immature skills in this domain, over time [63]. There is a particular interest in interrogating early parental concerns regarding autism in their child. A study noted a higher cumulative parental concern for ASD as early as 6 months of age in children who were later formally diagnosed with this neurodevelopment condition [64]. Professor Ouss highlighted a range of screening tools to identify children at high risk of ASD and described the Modified Checklist for Autism in Toddlers (M-CHAT) [65], which shows high sensitivity and specificity, with a 36 % predictive rate for ASD [66–68]. Early interventions for children with ASD are a relatively recent field of research with poorly defined evidence base, although the interest of proactive care and support is a main concern. She described the foundation for an enriched environment and growing evidence for parental intervention as the main vector of change, to optimise longer term neurodevelopmental outcomes for affected children. Several studies were presented that show the efficacy of parent mediated interventions for children with ASD, with reduction in social communication deficits, and improvements in cognitive and adaptive abilities. Results also revealed highly suggestive indications that parent-mediated interventions improved disruptive behaviours in early school-aged children [69]. Five main components of early intervention for children with, or at risk of, neurodevelopmental conditions were described, including parent coaching and daily intervention, modulating the frequency, duration and scope of interventions to meet specific needs, starting interventions as early as possible, and increasing parental sensitivity and response to a child's signals [70]. Children with lower skill range made greater progress in certain developmental areas, and it was highlighted that the most disadvantaged families with greater psychosocial stress would benefit from home sessions - even a low intensity intervention could provide significant gain [71]. Effective early interventions were described including the Naturalistic Developmental Behaviour Intervention (focussing on teaching skills in a natural setting and through typical adult-child interactions) and developmental strategies (focussing on supporting children's learning through interactions with other people, particularly caregivers). The evidence base for parent-mediated social communication therapies was described, showing a reduction in ASD symptoms and improvements in attention and communication over seven studies. This change was postulated to be driven by reduction in asynchrony between identification and responsiveness of parents to an autistic child's weaker social signals, driving an increase in the latter's initiation of social communication [72]. Professor Ouss ended by considering more nonspecific phenomenological targets and goals, including management strategies aimed at modifying early years spent in hospital, lack of socialisation, parental fear, early experiences impacting relationships with adults, lack of social mealtimes, and the inability to explore the environment at a preschool age.

6.2. Neurodevelopmental scales

Francesca Cumbo detailed a narrative review of neurodevelopmental scales that could be leveraged in evaluating cognition, adaptive function and behaviour children with SMA, to provide objective data to support clinical evaluations and research findings (see supplementary Table 2 and references [73–88] for specific details of each mentioned scale). The criteria for scale selection were noted in that tests offered had to be valid and reliable, applicable to children with the severe form of SMA and have sensitivity to developmental change. Neurodevelopmental scales that encompassed global development (evaluated through Griffiths III), motor and cognitive scales (Vineland Adaptive Behaviour Scales), behaviour and cognitive tools (Leiter 3, Raven, Wechsler Scales) and language and socio-communicative aspects were described. The Griffiths III was proposed as a clinical diagnostic test of a child's function from birth to 6 years of age, focussing on five (cognitive, motor, language, and social-emotional) developmental areas, providing indications for further diagnostic assessment. The tool was able to capture an evolving profile of strengths and weaknesses, obtained by plotting the graph of the quotients of each subscale and the overall level of development of the child by calculating a Development Quotient. Cognitive tools included the Leiter 3, described as a nonverbal intelligence test to provide equitable and inclusive assessment of cognitive ability across populations due to its language free component. She described the Wechsler Scales - WPPSI for preschoolers, WISC for school-age children, and WAIS for adults - to provide a comprehensive general intelligence assessment and identification of learning disabilities or neurodevelopmental disorders across different age groups and populations. Dr Cumbo urged caution when interpreting the results of the cognitive scales, with the Griffiths DQ emphasizing early development milestone acquisition, making it a robust but flexible tool to assess broad neurodevelopmental progress and early identification of delays and intervention planning. The Weschler IQ derived from a standardised comparison of age matched peers would give a more precise view of cognitive ability across the lifespan, used namely in older children and adults for educational placement, diagnosing learning disability and assessing intellectual potential. Adaptive functioning scales were reviewed. Here, one or more domains of conceptual, social or practical function had to be compromised to require support in an area. The Vineland and ABAS scales were compared with the ABAS considered best for general screening and functional assessment, of shorter duration and consisting of a questionnaire on conceptual, social and practical domains. The Vineland was noted as an in-depth clinical assessment for eligibility decision making, taking up to 60 min to complete and focussing on communication, daily living, socialisation and motor function questionnaires and an interview. A range of language scales were detailed including the Children's Communication Checklist 2, a standardized questionnaire designed to assess communication skills and identify language and social communication difficulties in children aged 4 to 16 years. It is commonly used to screen for pragmatic language impairments, ASD, and other communication disorders. Others included The Test di Fluenza Lessicale (TFL) a neuropsychological assessment used to evaluate verbal fluency, which reflects language production, executive functioning, and cognitive flexibility and the The Primo Vocabolario del Bambino (PVB) an Italian adaptation of the MacArthur-Bates Communicative Development Inventories (CDI). It is a parent-reported questionnaire designed to assess early language development in children aged 8 to 36 months. Socio-communicative scales included the CARS2-ST, to help distinguish ASD from other neurodevelopmental disorders and to assess severity of symptoms. This scale was described as quick and easy to administer (approximately 20–30 min), reliable and validated across different populations, useful for children as young as 2 years old and including both direct observation and caregiver input. The Social Communication Screening Questionnaire (SCQ) was detailed as useful to assess ASD in children $\geq$ 4y of age, used to provide quick and standardised measures for autistic traits for further clinical review. The Social Responsiveness Scales (SRS) was noted as a standardized questionnaire designed to identify social communication difficulties related to ASD, measure the severity of autism traits in children and adults, differentiate ASD from other conditions and be used from 2.5 years old. While the Autism Diagnostic Observation Schedule (ADOS), was considered the gold standard for ASD diagnosis, CARS was detailed by Dr Cumbo as a more practical tool due to its ease of administration, shorter duration, and accessibility, particularly useful for screening and severity assessment, making it a preferred option when time and resources were limited. Behavioural and

emotional scales were briefly highlighted including the Child Behaviour Checklist (CBCL) questionnaire, the Conners Parent Rating Scale (CPRS) and the Kiddie-S aimed at early diagnosis of affective disorders. Dr Cumbo detailed the strengths of the range of available tools including a comprehensive evaluation of developmental domains and standardised benchmarks, whilst acknowledging limitations including a lack of specificity for children with SMA and limited sensitivity to identify rapid clinical change. She ended by emphasizing the need to integrate motor and cognitive outcomes for affected children, to start the process of comprehensive neurodevelopmental assessment in this cohort and to foster collaboration and innovation to overcome barriers to assessment.

6.3. Early intervention in bulbar problems

Joana Ribeiro emphasized that bulbar dysfunction is a critical and well-recognized feature of SMA, particularly in early-onset forms. It leads to significant impairments in swallowing and speech production. The degeneration of lower motor neurons in the brainstem results in dysphagia, dysarthria, and an elevated risk of aspiration pneumonia, underscoring the importance of early identification and timely intervention [89]. With the advent of SMN restoring therapies, clinical management has improved, contributing to increased survival and, in many cases, the preservation of bulbar function—albeit with variable responses across patients. Continuous monitoring remains essential to optimize long-term outcomes. In the early forms of SMA—particularly among individuals with two copies of the SMN2 gene—dysphagia constitutes a major clinical concern [90]. Rapid progression of bulbar dysfunction is often observed, frequently necessitating alternative feeding methods within months of symptom onset. Clinical evaluations commonly reveal severe deficits in swallowing, and silent dysphagia is prevalent in untreated patients. These findings highlight the need for advanced instrumental diagnostic techniques, such as video-fluoroscopic swallowing studies (VFSS), to accurately assess bulbar involvement. In addition to routine clinical assessments and indirect indicators (e.g., failure to thrive and recurrent respiratory infections), the integration of standardized clinical tools—such as the Oral and Swallowing Abilities Tool (OrSAT) [91], the Neuromuscular Disease Swallowing Status Scale (NdSSS) [92], and the Clinical Evaluation of Dysphagia in SMA (CEDAS) [93]—may enhance the diagnostic accuracy and guide intervention planning. Joana Ribeiro also stressed the importance of early multidisciplinary intervention. This includes the involvement of speech and language therapists, dietary adjustments through nutritional supplementation and texture modification, and, when clinically indicated, the introduction of nasogastric or gastrostomy feeding. These strategies are vital to ensuring nutritional adequacy and preserving quality of life in affected individuals. In parallel, dysarthria has gained increasing recognition as a relevant clinical feature in SMA. It is typically attributed to craniofacial muscle weakness, progressive temporomandibular joint contractures, and laryngeal hypomobility. Clinical symptoms often include nasal or slurred speech, hypophonia (low vocal intensity), and vocal fatigue, all of which can adversely affect social interaction and educational participation. Intervention strategies may include targeted speech and language therapy, the use of augmentative and alternative communication (AAC) devices, and other assistive technologies to support and enhance communication. Moreover, Joana Ribeiro highlighted the need to better understand the relationship between severe bulbar dysfunction—rooted in lower cranial nerve involvement—and language deficits, which are classically associated with cortical regions in the dominant hemisphere. This interface warrants further exploration, particularly within the context of neurodevelopment in children with SMA. In conclusion, Joana Ribeiro advocated for a multidisciplinary approach to managing bulbar dysfunction in SMA. This approach should include early screening protocols, individualized speech and language therapy, nutritional support, the use of assistive communication technologies, and comprehensive developmental care. Such integrated strategies are essential to optimizing clinical outcomes, regardless of the specific therapeutic regimen employed. Ongoing research is crucial to refining current interventions and deepening the understanding of the long-term evolution of bulbar function in patients with SMA receiving disease-modifying treatments.

6.4. SMA neurodevelopmental and newborn screening programs

Didu Kariyawasam described the use of neurodevelopmental screening among children with SMA who inherit severe genotypes. The Ages and Stages Questionnaire (ASQ-3) is a widely used in clinical practice and can guide the need to refer for a diagnostic assessment, initiate early intervention and for monitoring [87]. She highlighted the need for a strengths-based approach to clinical research in this field, aligning with the needs and preferences of families. She presented data from a single centre cross sectional study, wherein clinical characteristics varied with modality of diagnosis, the number of survival motor neuron 2 (SMN2) copies and clinical status at initiation of SMN restoring therapy, associated with the magnitude and duration of survival motor neuron (SMN) deficiency [94]. Factors associated with no/low developmental risk included 3 or more copies of SMN2, diagnosis through NBS and clinical silent status, absence of bulbar dysfunction and greater motor function at therapeutic intervention, and parental wellbeing (i.e. absence of mental health condition and no distress).

SANDs had the potential to be amenable to modification by targeting bioecological factors of health. Namely, newborn screening and expedient initiation of treatment were postulated as central to targeting the neurodevelopmental window in children with or at-risk of early onset SMA. The incorporation of proactive developmental screening (with consideration of the ASQ3 as a suitable scale) for all children with or at-risk of a severe phenotype, alongside an integrated model of psychosocial support provided for families, was proposed as best practice.

6.5. Data collection and sharing

Aspects of data collection and sharing were described by Mariacristina Scoto and Rocio Garcia-Uzquiano as essential to fill knowledge gaps on the neurodevelopmental profile, assessment scales and interventions for children with SMA. Registries were described as a powerful and essential tool to facilitate shared information gathering and further clinical research [95,96]. A common data set for registries was proposed, with need to integrate developmental milestones, visual and auditory concerns and bulbar function alongside current elements. An example from the clinician-reported Spanish SMA registry was reviewed, with data collected for cognition, communication, understanding, behaviour and school setting [97]. Drs Scoto and Garcia-Uzquiano proposed a screening algorithm, ideally to start for children $<$ 2y of age. Clinical symptoms emerging within the first months of life were re-emphasised as key signs (with children capturing parental attention to prompt repetition of a specific ludic action). They described the need for clinicians to be trained in exploring developmental concerns with parents and communicating with them on an emerging cognitive phenotype in children with treated SMA. Developmental surveillance as part of routine clinical assessment was deemed essential to facilitating early intervention. They proposed a developmental screening battery with the ASQ3 [98](from 1–66months of age) to be conducted at each clinical visit (minimum 6 monthly), M-CHAT [65]for social communication to be done at a minimum of 18 months of age where concerns were present and preferably at 24 months of age. They also proposed the MacArthur Bates communicative development inventory [82]. Referral to specialist neurodevelopmental or neuropsychology services (as locally appropriate) for further assessment are recommended to achieve a formal neurodevelopmental diagnosis for children screening at risk. They acknowledged the need for further research on when to intervene i.e. before or after formal diagnosis of a neurodevelopmental condition and how to evaluate the effects of interventions.

7. Closing the loop: conceptual framework for socio-cognitive problems in SMA type 1 – D. Gómez-Andrés

Finally, a simplified pathogenic framework for SMA associated neurodevelopmental disorders was proposed. As illustrated in Fig. 1, we hypothesized that neurodevelopmental impairment in SMA results from the dynamic interaction of intrinsic genetic vulnerability, disease-mediated stressors and modifiable environmental influences.

8. Workshop deliverables and conclusions

The workshop allowed substantial and productive discussions and ended with propositions to further understand the impact of SMA on brain development and function.

Experts confirmed that a substantial proportion of the children with SMA type 1 followed by them, who would not have survived infancy without the new treatments, now manifest neurodevelopmental differences. These present in a range of ways that may affect speech, social interaction, behaviour and/or cognitive abilities. This is supported by recent basic and preclinical studies suggesting that low SMN protein levels may affect the developing brain in utero and eventually in early postnatal life [99].

Children with 1 or 2 copies of the SMN2 gene, those exhibiting early muscle weakness, or those who experience delays in initiating treatment appear particularly at risk. However, critical questions remain unanswered and require further investigation, including the actual prevalence of these neurodevelopmental issues in SMA populations, the existence of specific SMA neurodevelopmental profiles and their progression, as well as the contributing factors, such as the impact of current treatments.

A key focus of the workshop was addressing parents' concerns by improving neurodevelopmental assessments to facilitate the early detection of developmental differences. A consensus was reached on several critical areas:

First, the importance of early identification of potential difficulties and intervention was emphasized. Like other children with neurodevelopmental vulnerability or those with chronic neurological conditions, children with SMA can benefit significantly from close follow-up, preventive strategies, and timely interventions—particularly speech therapy. Clinicians should be proactive in identifying neurodevelopmental concerns by listening to parents and using appropriate screening or assessment tools. While a core screening strategy to monitor development in the clinic was agreed, further research and international collaboration were considered necessary to develop specific

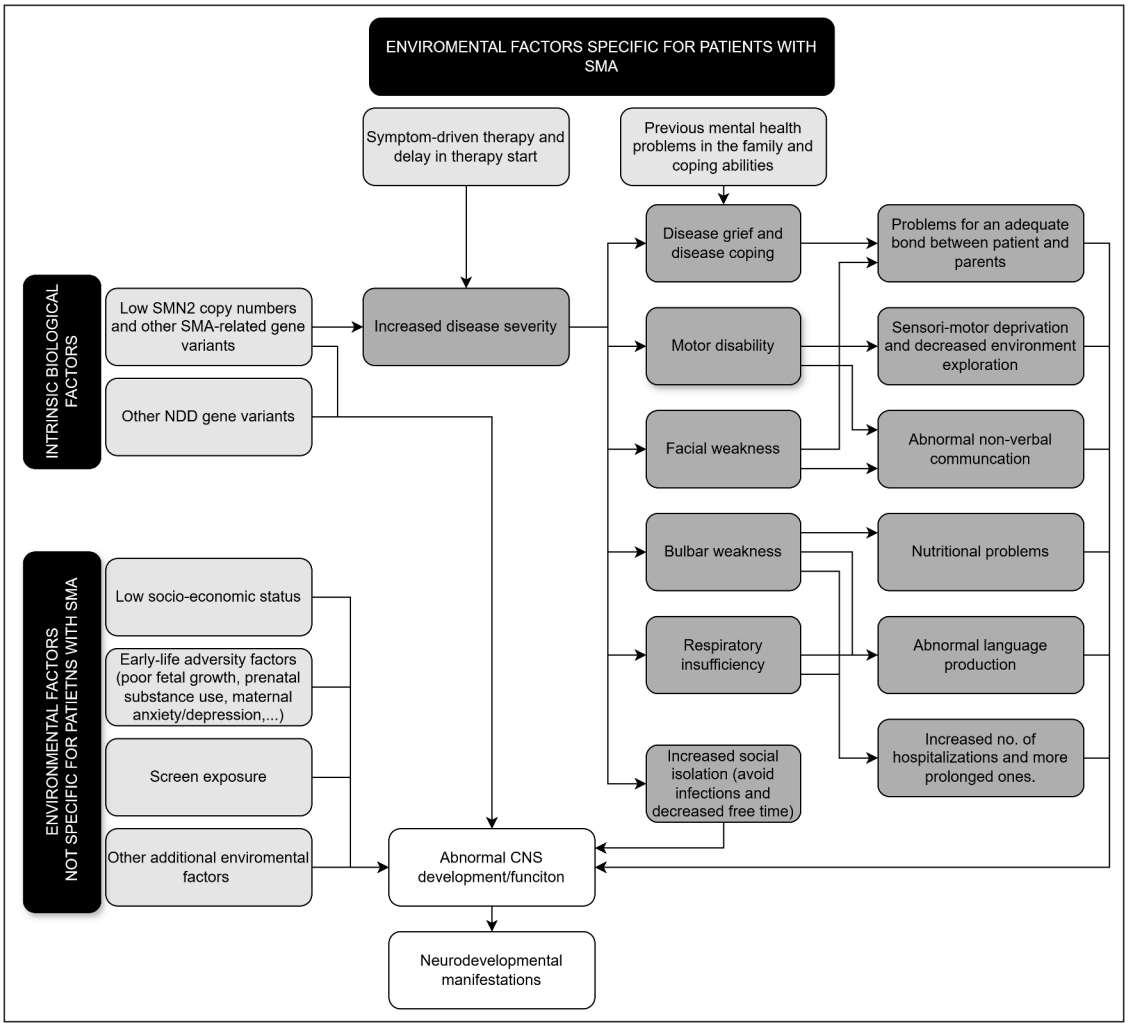

Fig. 1. Multifactorial model for neurodevelopmental impairment in spinal muscular atrophy. Intrinsic biological vulnerability) —low SMN2 copy number, other SMA related modifiers and non SMA neurodevelopmental genes—predisposes to abnormal central nervous system maturation. Disease mediated stressors (dark gray) — respiratory insufficiency, bulbar weakness, motor disability, symptom driven therapy delays and recurrent hospitalisation— amplify that vulnerability. Modifiable environmental factors (both specific for SMA patients and unspecific)) —sensorimotor deprivation, nutritional problems, early life adversity, low socioeconomic status, excessive screen exposure and family psychological distress—further perturb language and socio communicative development. Synergistic interactions across domains culminate in the spectrum of neurodevelopmental manifestations observed in SMA.

diagnostic and intervention guidelines.

Additionally, the careful interpretation of the existing assessment tools was highlighted as a crucial consideration. Standard neurodevelopmental tests may not always provide accurate results for children with severe motor, respiratory, or swallowing difficulties. Instead of relying on single-time-point evaluations, experts recommended longitudinal monitoring to better track developmental progress over time.

Supporting families emerged as another key priority. Advocacy groups underscored the need for family education and support, emphasizing the importance of guiding parents in recognizing early developmental challenges while focusing on their child's strengths. Families require clear information, psychosocial support, peer connections, and access to effective interventions to navigate their child's developmental journey.

Moreover, experts agreed on the need for global collaboration and research to better understand the neurodevelopmental aspects of SMA. There is a growing international consensus that cross-centre collaboration is essential to defining the epidemiology of neurodevelopmental differences and advancing both basic and clinical research. Understanding the underlying causes of brain dysfunction in SMA will require collective efforts, and incorporating families' perspectives in research and care strategies will be key to ensuring comprehensive support for affected children.

Participants also acknowledged the importance of a unified cognitive dataset within national registries to standardize data collection, as this would enhance both data quality and collaborative research efforts.

Finally, to further understand how SMA affects brain development, it was agreed to: 1) disseminate key workshop findings to increase awareness among professionals and families; 2) conduct an online survey addressed to international experts to assess the prevalence of neurodevelopmental disorders and study their characteristics and trajectories to identify specific SMA neurodevelopmental profiles; 3) develop diagnostic and care guidelines tailored to neurodevelopmental concerns in SMA; 4) establish Research Working Groups to explore both clinical and preclinical aspects of SMA, focusing on deep phenotyping, diagnostic tools, brain anatomy and neuro imaging, molecular biology, and biomarkers. These initiatives aim to advance SMA patient care while advocating for further scientific research to understand how and why neurodevelopmental differences occur in affected children. Addressing these research gaps is necessary to improve outcomes for children with SMA.

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Declaration of generative AI in scientific writing

During the preparation of this work the authors used ChatGPT 4 and 5 (OpenAI) and Notebook LMM (Google) in order to improve readability and language of some sections. After using these services, authors reviewed and edited the content as

CRediT authorship contribution statement

David Gómez-Andrés: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Michelle A Farrar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mireia Alvarez-Molinero:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Rocío Garcia-Uzquiano:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chiara Brusa:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Giovanni Baranello:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Susana Quijano-Roy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

S.Q.R. declares the following potential conflicts of interest: Speaker honoraria received from Biogen, Roche, Novartis, UCB; travel support from Roche, Biogen, UCB and Novartis; advisory roles with Novartis, Roche, Biogen, UCB, Scholar Rock. This author has participated in clinical trials and other studies sponsored by Biogen, Roche, and Novartis.

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Supplementary materials

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