Neuromuscular Disorders 56–57 (2025) 106252

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

284th ENMC International Workshop: Cognitive and behavioral abnormalities in pediatric DM1; what should we measure in preparation for clinical trials? Hoofddorp, The Netherlands, January 24-26 2025

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ARTICLE INFO

Keywords
ENMC workshop
Myotonic dystrophy type 1
Pediatric
Cognition and behavior
Clinical trials

ABSTRACT

In anticipation to clinical trials in pediatric DM1, the 284th ENMC workshop aimed to establish diagnostic and management protocols for CNS involvement based on international expert-consensus by 1) reviewing existing translational research findings on CNS involvement in pediatric DM1, 2) sharing current clinical and diagnostic approaches to CNS involvement in the international pediatric DM1 population and 3) discuss protentional CNS biomarkers relevant to future clinical and research applications in pediatric DM1. Patient and family perspectives on the impact on quality of life were considered. The workshop highlighted the complexity of the spectrum of CNS involvement from a research and clinical care perspective and confirmed the need for international harmonization of clinical assessment of cognitive-behavioral abnormalities. Consensus was reached on 1) disease classification based on age of symptom-onset and 2) a core neuropsychological assessment protocol to be used in clinical practice. Implications for trial design and further research are discussed.

1. Introduction

Eighteen participants from Italy, France, Germany, The Netherlands, Sweden, UK, Canada and the US met in Hoofddorp, The Netherlands, to discuss clinical and preclinical biomarkers and outcome measures for assessing central nervous system involvement in pediatric Myotonic Dystrophy type 1 (DM1), in preparation for clinical trials. The group comprised eight neurologists, two pediatric neurologists, four neuropsychologists, one speech-language therapist, two geneticists and one neurobiologists from six European centers, two centers in United States and one in Canada. The participants represented a broad spectrum of disciplines with both clinical and preclinical expertise in neuromuscular disorders, with a particular emphasis on myotonic dystrophies. One representative of the European Medical Agency (EMA) and two early career members were also present. In addition to the healthcare professionals, representatives of patients and patient advocacy organizations were also in attendance, including two from Italy and two from the Netherlands. Biopharmaceutical industry representatives from Dyne Therapeutics, Sanofi S.A. and Arthex were also invited to attend the meeting.

DM1 is the most common muscular dystrophy, with an estimated prevalence of 1 per 2100 when considering individuals with a CTG trinucleotide repeat expansion of 50 or greater [1]. Clinical heterogeneity in DM1 is high [2] with onset ranging from the prenatal period to late adulthood and with a multisystem involvement, with the brain often being affected [3]. The Central Nervous System (CNS) involvement in adult-onset DM1 is well recognized and is characterized by dysexecutive symptoms, visual-spatial abnormalities, and distinct personality traits

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https://doi.org/10.1016/j.nmd.2025.106252
Received 20 September 2025; Received in revised form 12 October 2025; Accepted 20 October 2025
Available online 21 October 2025
0960-8966/© 2025 Published by Elsevier B.V.

[4]. Excessive daytime sleepiness (EDS), primarily of central origin, is highly prevalent in DM1 [5–9] as well as sleep-wake cycle abnormalities [10]. Symptoms associated with central fatigue, apathy and EDS significantly affect the health-related burden perceived by adult patients living with DM1 [11,12]. The cognitive and behavioral abnormalities in DM1 are most likely multifactorial resulting from the combination of alterations in complex brain network interactions at a structural levels [13], altered white matter microstructural integrity and network organization [14,15] and tau splicing impairment [16].

While the CNS involvement has been extensively studied in adults with DM1 and to some extent there are diagnostic and management protocols in place in most expert DM1 centers, the approach to cognitive and behavioral abnormalities in children with congenital (CDM) and childhood-onset (ChDM) DM1 is still not standardized. The main cognitive and behavioral features of patients with pediatric-onset DM1 include developmental delay, intellectual impairment and autistic traits [17–24]. Children with DM1 also exhibit EDS [25], Sleep Related Breathing Disorders (SRBD) [26] and speech problems [27]. Motor and cognitive functions are differentially impaired in CDM and ChDM and their involvement may change throughout the progression of the disease. Children with congenital-onset are more severely affected from a motor, respiratory and nutritional perspective at birth, followed by a more prominent cognitive-behavioral involvement after 10 years of age [28]. Furthermore, currently there is no consensus as to which CNS outcomes are to be considered to assess changes over time and respond to treatment in children with DM1 [29,30].

The preliminary results from ongoing therapeutic trials with antisense oligonucleotides (DYNE-101), RNA-binding antibodies (Deldesiran), inhibitor of intracellular regulatory kinase (tideglusib) and anti miR (ATX-01) in adults with DM1 suggest that these treatments may modify the underlying pathophysiology and may result in functional improvement. In addition, some of these therapies may cross the blood brain barrier, potentially targeting CNS symptoms as shown in adult DM1. In childhood, intellectual impairment represents the leading source of disability [31] and could be a primary endpoint in trials conducted in CDM and ChDM. However, there is currently no consensus on the diagnostic and management protocols to be used in clinical and research settings. An additional critical consideration is that deeper understanding of the disease underlying causes and mechanisms could enhance the evaluation of symptoms and other clinical manifestations. Although pathophysiological processes are actively being investigated through cellular and animal models [32–39] there is an increasing need to advance translational research in the pediatric population to support the development and implementation of therapeutic trials in DM1 children.

Aims of the workshop were (i) to share current clinical approaches to CNS involvement in pediatric DM1 population among participants; (ii) to establish diagnostic and management protocols, based on expert consensus, to more effectively address cognitive and behavioral abnormalities in this population; (iii) to gain deeper insight into the CNS pathophysiology in pediatric DM1 population by reviewing existing translational research findings; (iv) to discuss potential CNS biomarkers relevant to future clinical and research applications in pediatric DM1.

During the workshop, all participants actively contributed to the review and evaluation of published evidence in each focus area as well as to the discussion of current practices within the group.

1.1. Session 1: Myotonic dystrophy, overview and focus on pathophysiology of CNS involvement

Nicholas Johnson (US), Genevieve Gourdon (France), Mario Gomes-Pereira (France), Eric Wang (US), Valeria Sansone (Italy), Federica Trucco (Italy and UK)

Prof Nicholas Johnson provided an **overview of the clinical and laboratory similarities and differences between adult-onset and pediatric-onset DM1.**

Patients with adult-onset DM1 generally have a normal neuromotor and cognitive development with symptoms appearing over the course of the disease with a relatively reduced CNS burden compared to pediatric-onset DM1. Core features in the skeletal muscle system include weakness and muscle wasting mostly affecting distal, cranial, and respiratory muscles. Myotonia is mostly present in adult-onset DM1 and preferentially affects hand/forearm muscles. In pediatric-onset DM1 a triphasic pattern of progression has been recognized (severe symptoms at onset, steady stage in childhood when CNS symptoms are prevalent, followed by an adult-like pattern of progression). The pediatric-onset DM1 is almost invariably characterized by abnormal neuromotor development.

Differences in the pathogenic mechanism of the disease have recently been recognized. In adult-onset DM1 the RNA splicing is more directly related to repeat instability and does correlate with muscle strength [40]. In children with DM1 the clinical symptoms seem related to DMPK expression in the first stages of development and to repeat instability thereafter. In children with DM1 the alternative splicing is more heterogeneous than in adults with DM1 as it changes with age [41]. For instance, recent findings have shown that the levels of DMPK are highest in infants and that the levels of the functional MBNL change across childhood development [30]. Further works on muscle tissue of children with DM1 are currently ongoing to determine the levels of RNA splicing across different stages of the disease and correlate them to clinical severity.

Dr Genevieve Gourdon, Dr Mario Gomes-Pereira presented **preclinical data on the brain disorder in their mouse model of DM1**

The **DMSXL mouse model**, carrying the human *DMPK* gene with a large CTG repeat expansion in both neuronal and non-neuronal cells, provides compelling preclinical evidence for brain involvement in DM1, with a clear regional specificity associated with functional abnormalities. The expression of the *DMPK* gene is broadly distributed in the brain but exhibits temporal and region-specific patterns in both humans and DMSXL mice. Importantly, MBNL and CELF proteins, which are key players in DM1 pathophysiology, also display distinct regional expression patterns that partially overlap with the distribution of *DMPK* RNA foci. During development, *DMPK* expression is particularly high in the brain during the perinatal period and early childhood, both in humans and in DMSXL mice and gradually decreases with age, suggesting that the early postnatal period represents a critical window for the onset of DM1-related brain dysfunction [42]. Toxic RNA foci, a hallmark of RNA toxicity, are widely distributed but show regional enrichment in the brain. In DMSXL mice, high levels of foci are found in the hippocampus, especially in the dentate gyrus and CA3, and in the brainstem, notably in cranial motor nuclei such as the dorsal motor nucleus (the nucleus of the 10th cranial nerve) and hypoglossal nucleus (the nucleus of the 12th cranial nerve).

There are also similarities between CDM and DMSXL newborns. They both show feeding difficulties, with reduced milk intake, and respiratory abnormalities which, in mice are mostly represented by obstructive apneas. DMSXL also exhibit delayed sensory-motor reflex acquisition, such as the righting and cliff-avoidance reflexes. With normal muscle development in this mouse model due to low *DMPK* expression in the muscles, these delays suggest central nervous system dysfunction, likely affecting regions involved in motor control, posture, and balance. On a molecular level, the hypoglossal nucleus, the nucleus of the 12th cranial nerve, a critical motor nucleus in the brainstem involved in apneas, shows a very high density of RNA foci associated with hyperexcitability in the hypoglossal motor neurons and splicing defects, which could explain the obstructive apneas observed.

In conclusion, given the widespread distribution of *DMPK* expression and the probable involvement of various brain regions in neurological dysfunction in CDM and ChDM, effective therapeutic strategies will need to target multiple brain regions. A successful treatment approach must address the brain's broad involvement to mitigate the full spectrum of DM1-related impairments.

Regarding the **identification of disease biomarkers** of CNS

involvement, *Dr Gomes-Pereira* highlighted that brain function depends on the intricate interplay between highly specialized **neuronal and glial cells**, which collectively regulate cognition, emotion, and sleep/wake cycles.

While mutant RNA accumulation and transcriptomic changes are well-documented in DM1 brains, the specific contributions of different cell types to brain pathology are not fully understood. Studies in DMSXL mice have shown that toxic RNA exerts a deleterious effect not only in neurons but more prominently in glial cells of young animals, leading to impaired astrocyte ramification [36] and delayed myelination (*unpublished data*). These glial phenotypes are associated with pronounced spliceopathy in cytoskeleton-related transcripts within astrocytes and oligodendrocytes, revealing a molecular signature of impaired differentiation, suggesting disrupted or delayed terminal differentiation [43]. Importantly, RNA toxicity in glial cells appears to compromise the intricate neuron-glia crosstalk, ultimately affecting neuronal physiology both in vivo and in mixed cell culture systems [36,44].

In addition to missplicing events, altered protein phosphorylation has emerged as an additional mechanism contributing to DM1 brain disease [45]. Interestingly, phosphorylation defects in DMSXL cells cannot be directly explained by splicing changes of the target proteins, suggesting a more complex pathophysiology [43]. Ongoing studies aim to further elucidate these mechanisms. Findings also suggest that the cerebellum (often overlooked in DM1 brain pathology) may play a role in disease pathophysiology. In DMSXL mice, abundant toxic RNA foci were detected in cerebellar Bergmann glia, a specialized astrocyte population. These glial abnormalities were associated with Purkinje cell hyperexcitability and cerebellum-dependent motor incoordination [44]. These results open new avenues for investigating cerebellar contributions to the neuropsychological manifestations of DM1. Dr Gomes-Pereira emphasized the critical need to target both neuronal and non-neuronal cells in future therapeutic strategies to effectively alleviate the complex neuropsychological symptoms of DM1.

Dr Eric Wang, Dr Federica Trucco and Prof Valeria Sansone focussed on **Excessive Daytime Sleepiness** and **central and respiratory sleep abnormalities**, discussing preclinical and clinical evidence.

Dr Wang gave an overview on the **sleep architecture** in healthy subjects and in patients with DM1 who often suffer from sleep-related disturbances, including hypersomnia and fatigue. While evidence supports neurofunctional and neurodegenerative changes occurring in adult onset DM1 (and DM2), neurodevelopmental alterations undoubtedly also playa a role in CDM, but existing data is still highly limited to characterize these changes. The classical two-process model for sleep regulation states that process C (circadian) and process S (sleep homeostatic drive) contribute to yielding the overall sleep state. In DM1, molecular and cellular pathways influence both processes. For example, core clock genes are mis-spliced in DM, and key tissues such as the choroid plexus, which regulates circadian rhythms, are uniquely vulnerable in DM1. Choroid plexus regulates cerebrospinal fluid production and it has been recently shown that this could modulate process C [46]. Finally, mis-splicing of neurotransmitter receptors could alter the way that downstream pathways respond to both processes and influence overall sleep regulation. Dr Wang concluded that while the field has made some progress to better characterize circadian rhythms and sleep in DM, much work remains to be done, particularly in CDM.

Dr Federica Trucco and Prof Valeria Sansone presented an overview on **respiratory function and CNS related sleep-related breathing disorders** in children with DM1.

Sleep disorders are often under recognized in children with DM1 yet representing a significant co-morbidity which, in turn, further adversely affects learning, memory, high-level cognitive processing and physical functioning, thereby exacerbating psychomotor and cognitive delays in DM1. The underlying mechanisms of sleep disorders in DM1 are complex and involve both respiratory alterations and intrinsic sleep/wake dysfunctions secondary to the CNS involvement (white matter abnormalities). Respiratory- and CNS-related sleep disorders are deeply intertwined and caused by respiratory muscle weakness, upper airway hypotonia and altered central control of breathing. The paradigm between the severity of restrictive lung disease and the onset and severity of SRBD is not as strict as in other NMD [47]. Sleep issues have been thoroughly described in adult-onset DM1 [48]. They include standard SRBD such as apnoeas/hypopnoea, hypoxia. Nocturnal hypoventilation is frequent in DM1 due to a reduced ventilatory response to overnight carbon dioxide (CO2) [47]. CNS-related sleep disorders such as Excessive daytime sleepiness (EDS), sleep/wake rhythm abnormalities, REM-related sleep abnormalities and other sleep disorders such as Periodic limb movements (PLM) and restless leg syndrome (RLS) [6,10,49,50]. Conversely, a broad characterization of sleep issues is lacking in pediatric DM1 [25,26,51,52]. Sleep issues were identified in 30 % to up to 66 % of pediatric-onset DM1 [51,53]. They consist mainly of SRBD such as hypopnoea and hypopnea [25,26,51], and EDS [51,53] affecting perceived patients' quality of life [25]. Sleep disruption caused by RLS and PLMs has also been reported in children with DM1 but systematic polysomnographic assessments with dosing of orexin and melatonin are currently ongoing (*personal, unpublished data*). Of note, the severity of sleep disorders does not strictly correlate with daytime symptoms such as daytime fatigue and EDS that can be present irrespective of a disrupted night [51].

Current clinical care recommendations suggest for the regular screening of EDS and SDB in children with DM1 using age-appropriate questionnaires, namely pediatric version of the Epworth Sleepiness Scale (P-ESS), Respicheck, Pediatric Sleep Questionnaire (PSQ); Pediatric Daytime Sleepiness Scale (PDSS) [19] and via sleep studies including CO2 monitoring. However there is a significant need to implement these diagnostic and management protocols in broad and homogenous cohorts of CDM and ChDM. This would allow standardized collection of data, and to identify the best outcome measures to use. Monitoring respiratory and CNS-related sleep disorders is key to instigate timely and appropriate treatment.

1.2. Session 2: Defining the spectrum of brain involvement in the pediatric age

Cornelia Kornblum (Germany), Sylvia Klinkenberg and Dirk Sweere (the *Netherlands), Isabelle Gaudet (Canada)*. Session moderated by Dr Guillaume Bassez (France), who brought his expertise in the field of Myotonic Dystrophies.

Prof Cornelia Kornblum presented an overview of the literature on **neuroimaging findings** in DM1 patients (children and adults).

Cross-sectional studies in DM1 demonstrated ventricular enlargement, brain atrophy, and focal subcortical and cortical gray matter reduction in various brain regions with no disease-specific patterns. White matter lesions are frequent and predominantly located in frontal and anterior temporal lobes. Thinning or atrophy of the callosal body has been reported most frequently in congenital DM1 but is also present in adult-onset forms. Voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) show a severe and widespread degradation of white matter including involvement of association fibers (e.g. limbic system), commissural fibers (e.g. callosal body), and projection fibers. In general, white matter changes are more prominent than grey matter changes at least in adult-onset DM1. Gray matter more than white matter changes are reported to be slightly progressive [54] which may hint to a neurodegenerative disease component. White matter affection however seems to progress to almost the same extent in healthy controls and patients with no disease-specific deterioration. These findings suggest rather stable white matter changes over time [54,55]. However, the natural history of structural brain changes is not fully clear since findings are partially controversial. There is e.g. also some data showing deterioration of white matter changes over time [56]. Cerebral atrophy, callosal hypoplasia, brain malformations and diminished white matter volume can be present in congenital DM1 and these findings are even detectable in prenatal (fetal) MRI in severe cases [57]. In studies on

pediatric DM1, a majority of congenital patients showed white matter affection [58]. A distinct pattern of progressive focal grey matter volume decrease was detected in a cohort of children using a VBM technology. These findings were interpreted as of neurodevelopmental origin along with the potential existence of an additional neurodegenerative process [55]. Brain imaging data in general is difficult to interpret since applied imaging techniques are variable, patient cohorts are usually small and heterogeneous, matched control groups are often missing, and longitudinal data is highly limited especially in children. This may be a crucial point in designing clinical trials targeting the brain in the adult population. Overall, though there is an exponential increase of studies on brain imaging in the adult DM1 population, brain imaging data on pediatric DM1 is still highly limited.

In addition to the literature on neuroimaging findings, *Dr Isabelle Gaudet* presented an overview of 24 studies reporting on **neuropsychological assessment** findings in individuals with ChDM, spanning 11 countries and a total of 416 patients (*Gaudet* et al.*, under submission*).

A significant heterogeneity in the tools used to assess various cognitive and behavioral domains was observed, which complicates cross-study comparisons. Intellectual functioning was the most frequently assessed domain, typically measured using Wechsler Intelligence Scales. Impaired IQ scores were a consistent finding across studies. Other domains frequently impaired regardless of age groups include visuospatial abilities, attention and executive functions, social cognition, and adaptive skills, though these have been assessed using different instruments. Language abilities consistently showed impairments in adulthood, while results in pediatric populations varied – suggesting that developmental trajectories may differ by domain. One of the key challenges highlighted by the review is the limited number of longitudinal studies ($n = 2$), which hinders our understanding of how cognitive and behavioral functions evolve over time. This limitation is compounded by the fact that many tests are age-related and not easily translate to adult assessments, making comparisons over time even more difficult.

The evidence available so far does not provide clear support for significant neurocognitive decline in adults. However, only 7 studies focused on adult populations and none of them included longitudinal follow-up. This gap leaves uncertain whether childhood-onset DM1 involves neurodegenerative processes, in addition to neurodevelopmental impairments. Overall, the heterogeneity in tools and approaches used underlines the need for standardized assessments to better characterize the neurocognitive profile and progression in childhood-onset DM1 patients.

Dr Sylvia Klinkenberg and Dirk Sweere concluded with a brief **overview of the neuropsychological assessment procedures and associated neuropsychological findings in the Netherlands** from a clinical care perspective.

The heterogeneity in use of neuropsychological instruments in the scientific literature that was reported by *dr Isabella Gaudet* was demonstrated by an overview of assessment procedures used in clinical practice in The Netherlands. Wechsler intelligence scales are consistently used for assessment of global intellectual functioning. For additional neurocognitive evaluation, sixty-two different (sub)tests were used in fourteen clinical sites (mostly rehabilitation centers), spanning over 10 cognitive domains that were inconsistently assessed in the patient groups [21]. The heterogeneity in the protocol of tests was recognized by countries representatives as the main limitation. Besides assessment of cognitive deficits and behavioral pathology (diagnosis of neurodevelopmental and psychiatric comorbidities), the need for follow-up of the abilities to cope with psychosocial challenges in daily life, school and interacting with peers (i.e. psychosocial adjustment) [59,60] was discussed as a relevant factor for quality of life during childhood.

Overall, in this session it was concluded that international harmonization of neuropsychological assessment protocols is necessary to gain a better understanding of brain involvement in pediatric DM1, given the rarity of the disease and the heterogeneity seen in neuro-imaging and neuropsychological findings. From a clinical-scientific perspective, sample sizes are generally small. Neuroimaging could provide more insight into the relation between brain-pathology and cognitive development and cognitive functioning which may have important implications in designing clinical trials.

1.3. Session 3: Current protocols and procedures

Valeria Sansone, Susanna Pozzi (Italy), Dirk Sweere, Dr. Hilde Braakman (The Netherlands), Kiera Berggren (USA), Nicholas Johnson (USA), Nathalie Angeard (France), Julie Eisengart (USA), Nikoletta Nikolenko (UK).

Session moderated by Dr. Guillaume Bassez (France), who brought his expertise in the field of Myotonic Dystrophies assessment. This was a two-step process. The first area of focus was to examine the tests and procedures that have been previously described in literature for this population along with reported results. The second area of focus involved reviewing the tests and procedures currently in use across participating sites at the workshop.

Dr. Susanna Pozzi, Dirk Sweere, Dr. Hilde Braakman and prof Valeria Sansone presented the results from a **systematic literature review and one international survey** on the use of clinical protocols and scales to assess for cognition and behaviour in the international pediatric DM1 population.

For the literature review, all the studies reporting cognitive and behavioral assessment in pediatric DM1 published between 2006 and 2024 as documented by Elsevier and PubMed were analyzed. Overall, 25 articles were considered. Overall, the findings emphasize the importance of multi-center collaboration to increase sample sizes and to enhance the generalizability of results. The need to longitudinal studies is underscored. Although there is consensus regarding the assessment tools used to evaluate global cognitive functioning and IQ, no standardized agreement currently exists on instruments for assessing specific cognitive domains. The prevalence of disharmonic or inconsistent intelligence profiles in pediatric DM1 is significant and makes the definition of a cognitive and behavioral profile more complex. Search strategies and results will be published in a separate paper.

Prior to the meeting a structured digital survey was drafted to investigate the instruments currently used for evaluating cognitive and behavioural aspects in pediatric DM1 patients across the international clinical setting represented at the ENMC workshop (Appendix 1). Instrument reaching a consensus of ≥50 % among responders were identified. The Wechsler Intelligence Scales were the most frequently endorsed tools for evaluating general cognitive abilities (67–72 %). For assessing general developmental abilities, the Bayley and Vineland Adaptive Behavior Scale (VABS) were supported by 53 to 59 % of participants. The Behavior Rating Inventory of Executive Function (BRIEF) scale [61] achieved a 58.5 % consensus for evaluating executive functions, while the Child Behavior Checklist (CBCL) [62] was the preferred tool for assessing behavior, emotional functioning and social cognition, with a 66 % agreement. In the domain of quality of life assessment, the Pediatric Quality of Life Inventory (PedsQL)[63] reached the highest level of consensus at 72 %. Within the language category, the Peabody Picture Vocabulary Test (PPVT) shows a consensus by 44 % of responders. For the assessment of attention, the Test of Everyday Attention for children (TEA test) received 47 % consensus. In the autistic spectrum assessments domain, the Autism Diagnostic Interview – revised (ADI-R test) reached a 44 % level of agreement. Regarding long-term memory, the Rey-Osterrieth Complex Figure Test (ROCF test) and Rey Auditory Verbal Learning Test (RAVLT) were considered relevant by 27 % of participants. In the sleep domain, both the Pediatric Sleep Questionnaire (PSQ) [64] and the Pediatric Daytime Sleepiness Scale (PDSS) [65] were identified as relevant by 33 % of responders. Additionally, for evaluating disease burden, the Congenital and Childhood Myotonic Dystrophy Health Index (CCMDHI) [66] was the only instrument showing a 33 % relevance.

As highlighted in recently published care recommendations [19], all participating centers emphasized the importance of multidisciplinary care. In addition to reaching consensus on which assessment tools to utilize, another critical issue discussed was the timing of evaluations. Specifically, when and how often assessments should be conducted. There was general agreement that regular follow-up is essential to ensure consistent monitoring and timely intervention. While annual follow-ups (every 12 months) were considered as the minimum requirement, a more frequent schedule—every six months—was recommended for optimal outcomes, particularly in younger children where developmental trajectories may change more rapidly compared to typically developing peers. This approach facilitates early identification of emerging developmental concerns and supports the timely implementation of appropriate interventions.

Overall, the results of the survey underscore the current lack of international consensus regarding the specific outcomes that should be assessed to document CNS involvement in pediatric DM1 as well as to monitor longitudinal changes in cognitive and behavioral functioning in this population. The findings highlighted the importance of reaching a consensus on the classification of pediatric DM1, which serves as a foundation for the development of new treatment protocols and guiding clinical practice. In preparation for clinical trials, it is particularly essential to identify and standardize the use of assessment tools, across their various versions, that are capable in detecting specific disease-related neuropsychological and behavioral features. Priority should be given to the instruments that demonstrate sensitivity to change, feasibility of use in this population, and reliability as outcome measures in both clinical and research settings.

In the context of cognitive-behavioral development and detecting longitudinal changes in cognitive and behavioral functioning in clinical trials, *Dr Nicholas Johnson* presented his clinical and scientific experience with longitudinal cognitive-behavioral data i.e. intelligence quotient scores, the Vineland scale (adaptive functioning), the BRIEF questionnaire (executive functions) and parent-reported measures of autism spectrum features and excessive daytime sleepiness. Based on the clinical experience from the ongoing **international observational natural history studies** (TREAT-CDM – *"Trial readiness and endpoint assessment in congenital myotonic dystrophy"*, NCT03059264 and ASPIRE-DM1 – *"Assessing pediatric endpoint in DM1"*, NCT05224778), Dr Johnson stressed that subtle differences as quantified in raw scores of the instruments are not necessarily visible in standardized scores, but in some cases, do reflect notable changes in daily life functioning and quality of life. This may have important implications in designing natural history studies and quantification of significant change in cognitive-behavioral functioning in the context of clinical trials. It is important to investigate an instruments sensitivity to change and to define a cut-off for clinically relevant change over time, based on empirical data.

In addition to assessment of intelligence, specific cognitive impairments and behavioral functioning, *Dr Kiera* Berggren stressed the importance of assessment of **language and verbal communication skills** in children with DM1.

Reduced communicative ability is a significant concern for parents of children diagnosed with congenital or childhood-onset myotonic dystrophy type 1 (DM1). This issue encompasses various levels of function, including cognition, language, and motor speech planning and production. Language acquisition is notably delayed, with about one-third of individuals presenting substantial expressive language delays or remaining non-verbal beyond the typical age of language acquisition. Social-pragmatic issues are prevalent in approximately half of children with DM1, affecting communication through reduced conversational initiation, limited topics of interest, and repetitive behaviors. Flaccid dysarthria is a common feature, affecting 83–100 % of children who communicate verbally, and speech intelligibility is closely tied to orofacial strength as well as other speech subsystems. The communication impairments in pediatric-onset DM1 remain under-researched, particularly regarding the impact of cognitive and linguistic deficits. Standardized testing proves challenging. A child-friendly picture description task may offer a valuable method for documenting speech and language in a more naturalistic context throughout development. Clinical utility and feasibility were demonstrated in a pilot study involving five children aged between 0.98 and 2.05 years (*unpublished data*).

Dr Nathalie Angeard presented a brief overview of the literature on neuropsychological assessment and the spectrum of **brain involvement in children with Duchenne Muscular Dystrophy (DMD)**.

This was important to learn from previous experiences with children having similar difficulties yet with different neuromuscular conditions in whom there are trials already ongoing and targeting muscle dystrophin. Similarities in scientific challenges with pediatric DM1 research were explored. Similar to pediatric myotonic dystrophy type 1 (DM1), the DMD phenotype is not only characterized by motor deficits but also by a more generalized developmental delay, with considerable variability observed across affected individuals. Overall, individuals with DMD exhibit a full-scale intelligence quotient (FSIQ) of approximately one standard deviation below the population average [67]. While visuo-perceptive abilities are generally preserved, verbal abilities are frequently impaired. More specifically, oral language processing, short-term memory, working memory, cognitive flexibility, and, more broadly, executive functions, are identified as particularly vulnerable domains [68]. The neuropsychological area of social cognition has recently been investigated, revealing impairments in theory of mind and facial recognition, independent of the general level of intellectual functioning [69]. Significant heterogeneity in the procedures and instruments used to assess cognitive and behavioral functioning is reported in the Duchenne literature. In this context, the recent development of a theoretical framework, i.e. the Big Ten of Duchenne model [70] may be helpful for international harmonization of assessment procedures to cover all domains of importance concerning cognition, behavior, emotion and learning.

Overall, the current challenges faced in international harmonization of assessment procedures are not unique to the pediatric DM1 field. The development of a theoretical model characterizing the spectrum of brain involvement in pediatric DM1 could serve as a foundation for the standardization of assessment protocols, similar to recent advances observed in the DMD field.

Dr Julie Eisengart further emphasized the challenges associated with the use of neuropsychological assessment in rare pediatric diseases.

Neuropsychological assessment is crucial across multiple stages of the clinical pathway and supports the characterization of the disease's natural history, clarifies the clinical response to therapies, informs the optimal timing of interventions, and contributes to the development of targeted supportive strategies [71–73]. At the individual level, it can aid in identifying complications related to disease progression. However, this type of assessment requires a shift in how cognitive and functional outcomes are traditionally conceptualized and measured. Functional impairments in rare diseases are often influenced by factors beyond the direct involvement of the central nervous system (CNS), and early signs of neurodegeneration in children may be subtle, making early detection particularly challenging [72,74,75]. In this context, there is a clear need for sensitive and flexible assessment tools capable of capturing the complex and evolving manifestations of rare diseases [76]. It is crucial to recognize that low test scores may reflect a wide range of underlying mechanisms and therefore require careful interpretation within the clinical and research contexts. This complexity calls for a broader and more nuanced understanding of "function," so that outcome measures can be both clinically meaningful and relevant to the patient's quality of life. Within this framework, the active involvement of families and communities is essential in shaping therapeutic goals and developing appropriate assessment tools [76–79]. The progressive nature of functional disabilities in rare diseases has an impact on family systems, which deserve greater recognition and representation in both scientific literature and treatment development processes [75,76,80,81].

Dr Nikoletta Nikolenko from London UK concluded with an overview of the **lessons learned from conducting clinical trials and natural history studies in Congenital Myotonic Dystrophy** (CDM). These included Phase 2 and Phase 2/3 clinical trials both sponsored by AMO Pharma and the CARE-CDM cohort study funded by Muscular Dystrophy UK.

Key points of discussion included the importance for early collaboration between clinical teams and patient organizations during the design and setup of both interventional and observational studies. This engagement facilitates effective outreach and helps address specific needs of patients and their caregivers, many of whom are themselves affected by DM1, including mobility challenges and other disease-related symptoms.

Dr Nikolenko stressed the ethical considerations surrounding the consent process for research participation. Parental responsibility and power of attorney should be addressed in advance. Several levels of informed consent may be required for both caregivers and patients, incorporating suitable consent procedures tailored to the comprehension abilities of the participants. Allowing sufficient time for consenting processes is strongly advisable to ensure ethical and informed participation. Another key point in the design of clinical trials is the comprehensive documentation of non-pharmacological interventions such as speech therapy, physiotherapy, and occupational therapy, which similar to concomitant medications, play significant role in impacting on patient's condition. Additionally, long school breaks should also be considered when designing a clinical trial as they may impact interpretation of results.

Flexibility in study protocols and reporting results is essential. For example, patient phobias and sensitivities may necessitate encouragement and patience before assuming non-compliance. Clinical and physical outcome measures should be age-appropriate and symptom-specific with simple, single-task assessments being preferable. Some clinical assessments, such as spirometry and manual muscle testing, may be unreliable due to patients' clinical features and comprehension levels. Finally, regarding cognitive assessments, Dr Nikolenko recommends using brief, gamified, touchscreen-based cognitive tests with adaptive elements to accommodate the variability in cognitive functioning. Input from schools and therapists is valuable for quality-of-life assessments and other questionnaires, particularly when primary caregiver is also affected by DM1. Furthermore, assessment and reporting of quality-of-life in caregivers and parents of CDM patients could provide valuable insights into broader impact of this disease on families and support systems.

2. Conclusions

The workshop yielded three principal outcomes: (i) consensus was reached on an official classification for DM1 in the pediatric population; (ii) agreement was established on the core neuropsychological assessments to be evaluated, stratified by age, in the pediatric DM1 population; (iii) the perspectives of patients and families strengthened the clinical and research group's understanding of the disease burden in this age group, while also highlighting existing gaps in assessment approaches and current care.

2.1. Disease classification (Fig. 1)

Myotonic Dystrophy is a very heterogeneous disorder presenting anytime from prenatal period until late adulthood. The early-onset presentation, within 1 month from birth, is to be defined Congenital Myotonic Dystrophy. This presents with variable life-threatening symptoms ranging from respiratory distress, feeding difficulties, hypotonia, arthrogryposis and failure to thrive, brain malformation and organomegaly in some cases. The agreed acronym is CDM. Although clinical presentation can vary from this early-onset congenital presentation, with some children presenting at around age 2 or 3 while others later on in childhood or early adolescence, consensus was reached the term childhood onset Myotonic Dystrophy, with the acronym being ChDM should be used to refer to all individuals who develop symptoms between 1 month and 18 years of age. This classification does not preclude the concept that, in most cases after the age of 12 and more typically from 16 years onwards, the clinical manifestations at onset increasingly resemble those of the adult-onset phenotypes. This also reflects splicing defect patterns (ref Johnson). Yet, to simplify ontology, classification and inclusion into clinical trials or observational studies there is a need to harmonize nomenclatures and definitions. Ongoing research and future findings are expected to provide additional evidence that may enable further refinement of this classification.

2.2. Neuropsychological assessments

Based on the comprehensive literature review, current clinical practices and expertise of the participating members, a consensus was reached on the core neuropsychological assessments recommended for documenting and monitoring cognitive and behavioral abnormalities in pediatric DM1. Emphasis was made on selecting tools that are validated and available across multiple languages to ensure broader applicability. Particular attention was given to identifying measures that could be administered across different age groups, thereby facilitating longitudinal comparisons where feasible. To address variability in site-specific resources and clinical capacity, the recommended assessments were categorized into two tiers: **mandatory** and **optional (nice to have)**. Mandatory assessments were those deemed feasible and practical by the majority of participating centers and are expected to yield robust, comparable datasets across sites. Optional assessments, while considered valuable, may be implementable only at selected sites due to resource constraints but were still recommended for inclusion when possible, given their potential to contribute meaningful data.Figs. 2 and 3 summarize the selected assessments based on age for each cohort, and onset of the disease (congenital and childhood).

Dr Kornblum's review highlighting the absence of standardized protocols for performing brain MRI in pediatric DM1 patients prompted a broader discussion on the need for a more proactive approach neuroimaging in this population. Given that DM1 is fundamentally a central nervous system (CNS) disorder, participants emphasized that investigations should routinely include structural brain imaging, such as MRI, as a foundational component of clinical assessment. Concerns regarding the requirement for general anesthesia in DM1 children undergoing MRI were addressed. It was proposed that when sedation is considered necessary, the child should first be evaluated by an anesthesiologist. If no significant clinical contraindications are identified, brain MRI should be prescribed as part of routine evaluation, particularly to document structural abnormalities that may contribute to the individual's cognitive and behavioral phenotype. Available studies involving children over the age of six rarely report the need for sedation during MRI, with the exception of patients with severe congenital DM1 (CDM), in whom imaging is often performed in the neonatal period while still intubated and under intensive care. Furthermore, clinical experience from other pediatric CNS disorders involving comparable levels of disability supports the feasibility and value of routine brain imaging in this context [82].

2.2.1. Core assessment of global cognitive functioning and adaptive skills

For patients aged 0–3 years, assessment of early milestone development and development of adaptive behavior using the Bayley-III scales and Vineland Adaptive Behavior Scales (VABS) is advised. These instruments allow for comprehensive analysis of developmental strengths and weaknesses, including adaptive behavior, cognitive development, language development, motor development and social-emotional development. For patients aged 4–18 years, assessment of global intellectual functioning using the Wechsler intelligences scales is advised. The Wechsler intelligence scales are widely used in the countries

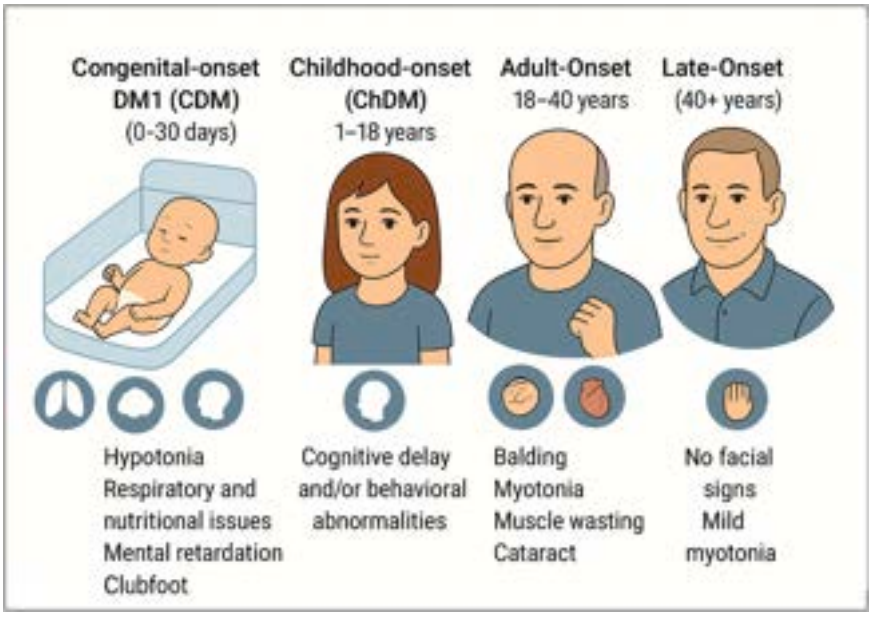

Fig. 1. Disease classification and main clinical features.

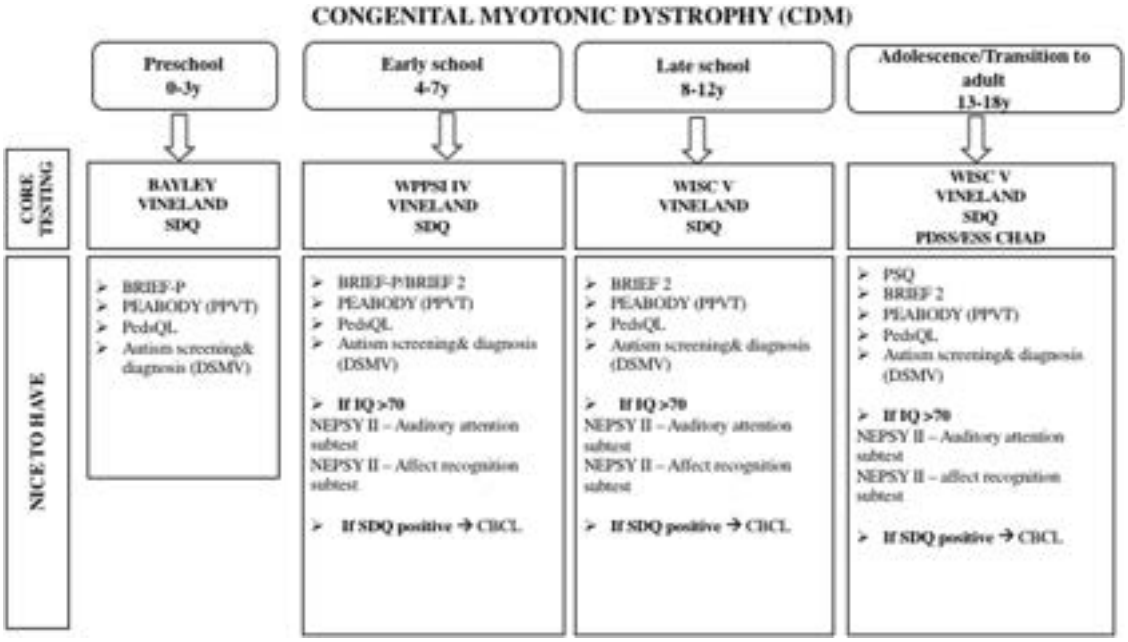

Fig. 2. Assessment Protocol for Congenital Myotonic Dystrophy (CDM).
Note. Bayley = Bayley Scales of Infant and Toddler Development, Vineland = Vineland Adaptive Behavior Scales, SDQ = Strengths and Difficulties Questionnaire, BRIEF-*P* = Behavior Rating Inventory of Executive Function – Preschool version, BRIEF 2 = Behavior Rating Inventory of Executive Function – Second edition, PPVT = Peabody Picture Vocabulary Test, PedsQL = Pediatric Quality of Life Inventory, DSM-*V* = Diagnostic and Statistical Manual of Mental Disorders – Fifth edition, WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence – Fourth edition, NEPSY-II = NEPSY – Second edition, CBCL = Child Behavior Checklist, WISC-*V* = Wechsler Intelligence Scale for Children - 5th edition, PDSS = Pediatric Daytime Sleepiness Scale, ESS CHAD = Epworth Sleepiness Scale for Children and Adolescents, PSQ = Pediatric Sleep Questionnaire.

represented in the ENMC meeting, is consistently used in the current scientific literature on brain involvement in DM1 and allows for comprehensive analysis of cognitive strengths and weaknesses.

2.2.2. Assessment of behavioral functioning and emotional well-being

A two-step approach to assessing problems in behavioral and emotional functioning and well-being is recommended. Administration of the Strengths and Difficulties Questionnaire (SDQ) [83] is strongly recommended in all pediatric DM1 patients. The SDQ is a brief questionnaire (available as parent-report, teacher-report and self-report questionnaire) that allows for global screening of emotional and behavioral problems in children aged 2 – 17 years. The instrument consists of 25 items and is translated in multiple languages, which makes the instrument easy to administer and suitable to use in standardized international clinical follow-up (see www.sdqinfo.org for the questionnaires and explanation of the scoring procedure). Interpretation of the total problems scale, ranging from 0 to 40 points, as a screening for clinically relevant problems is recommended. In case of a total score

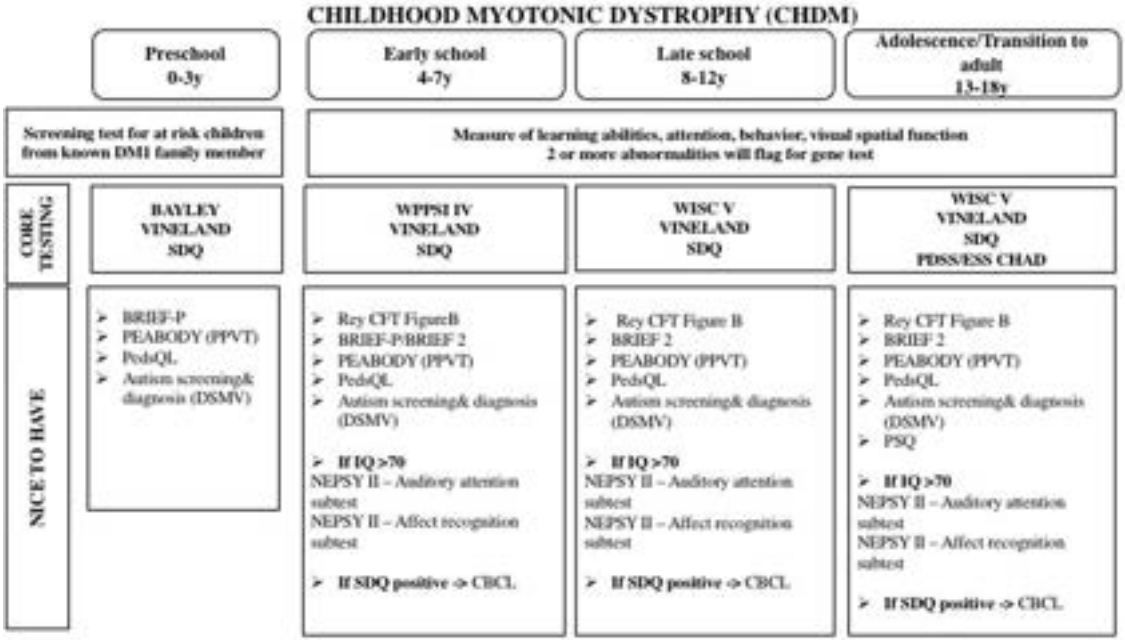

Fig. 3. Assessment Protocol for Childhood Myotonic Dystrophy (ChDM).
Note. Bayley = Bayley Scales of Infant and Toddler Development, Vineland = Vineland Adaptive Behavior Scales, SDQ = Strengths and Difficulties Questionnaire, BRIEF-*P* = Behavior Rating Inventory of Executive Function – Preschool version, BRIEF 2 = Behavior Rating Inventory of Executive Function – Second edition, PPVT = Peabody Picture Vocabulary Test, PedsQL = Pediatric Quality of Life Inventory, DSM-*V* = Diagnostic and Statistical Manual of Mental Disorders – Fifth edition, WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence – Fourth edition, Rey CFT = Rey Complex Figure Test, NEPSY-II = NEPSY – Second edition, CBCL = Child Behavior Checklist, WISC-*V* = Wechsler Intelligence Scale for Children - 5th edition, PDSS = Pediatric Daytime Sleepiness Scale, ESS CHAD = Epworth Sleepiness Scale for Children and Adolescents, PSQ = Pediatric Sleep Questionnaire.

above the cut-off of 14 points, further assessment of emotional and behavioral problems and possible psychiatric comorbidity using the Child Behavior Checklist (CBCL) [62] is strongly recommended for further assessment of psychopathology and psychiatric comorbidity. Additional administration of the Pediatric Quality of Life Inventory (PedsQL) [63] may be considered based on availability of the instrument and normative data in the country of origin.

Based on the reported increased prevalence of Autism Spectrum Disorder (ASD) in the pediatric DM1 phenotype [84], screening for ASD is strongly advised in all patients using validated instruments based on normative data in the country of origin. In case screening is indicative for possible presence of ASD further diagnostic procedure based on the DSM-5 classification criteria is recommended, following the national clinical guidelines in the country of origin (for example using a structured clinical interview).

2.2.3. *Screening for sleep disorders*

Timely screening for sleep disorders after the age of 13 years is strongly recommended based on current clinical care recommendations [19]. For this purpose, consensus was reached on the use of the Pediatric Daytime Sleepiness Scale (PDSS) [65] and Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) [85].

2.2.4. *Additional specific cognitive assessments*

Additionally, based on patient characteristics and availability of instruments in the clinical setting, further assessment of cognitive functioning may be considered. Additional recommended instruments cover the assessment of executive functioning (Behavior Rating Inventory of Executive Function; BRIEF), sustained attention (NEPSY-II auditory attention subtest), visuo-constructional/visuo-motor skills (Rey-Osterrieth Complex Figure Test; ROCF test/ Rey-Osterrieth Complex Figure B test (ROCF-B test)), receptive vocabulary (Peabody Picture Vocabulary Test; PPVT) and social cognition (NEPSY-II Affect Recognition subtest) as core cognitive deficits in DM1. For the Rey-Osterrieth Complex Figure administration of the 'Figure B' is recommended due to the lower visuo-spatial complexity, as compared to the 'Figure A' that is generally used in clinical practice [86]. Assessment of working memory and information processing speed is covered in the Wechsler intelligence scales.

2.3. *Family representatives experience and perceived burden*

Family representatives shared their personal experience of caring for children with congenital- and childhood-onset DM1, providing valuable insights into the challenges faced by families affected by this condition. Although continuous communication between clinicians, patients and their families typically informs disease management, the structured setting of the workshop provided a unique opportunity for more focused and scientifically grounded discussion of these experiences. Their testimonies contributed significantly to the clinical and research dialogue, highlighting critical areas of unmet need.

The parents described a multifaceted range of cognitive, emotional, behavioral, and social challenges that impact not only the children but also the broader family. According to families, the cognitive difficulties faced by children with DM1—such as problems with attention, concentration, task organization, and reasoning—pose a major burden. These issues often require additional support, including visual aids and individualized teacher assistance, and contribute to slower academic progress, making it difficult for affected children to keep up with peers at school. Emotional and behavioral challenges were also emphasized. Children frequently experience heightened sensitivity, emotional dysregulation, and difficulty recognizing or managing emotions which manifest as frustration, anxiety, anger and irritability. These affective symptoms substantially reduce quality of life and complicate daily caregiving responsibilities, often straining family dynamics. Social and relational challenges, including limited emotion expressiveness reduced ability to engage in long conversations, social isolation, and a preference for solitude, are also commonly reported by families. These impairments hinder the development of peer relationships, further contributing to

isolation and limiting participation in age-appropriate social contexts. In addition, families emphasized the high level of dependency children with DM1 have on their caregivers, requiring close supervision for daily routine and self-care. Children also struggle with participation in group activities and school events, limiting their social and recreational engagement. The combination of cognitive, emotional, and social difficulties creates a significant burden for families, leading to increased stress in managing daily care.

To address these challenges, families advocated for coordinated multidisciplinary support system, particularly within the school environment, to meet the child's evolving needs. They also highlight the need for structured evidence-based care protocols to guide interventions, nursing procedures, and clinical follow-up schedule, ensuring care is comprehensive and tailored to each child's specific needs. This approach is crucial for improving the quality of life for both the child and their family, fostering an environment that supports growth, learning, and emotional well-being. Finally, families indicate several factors that could enhance the healthcare process, including managing stress-inducing situations such as blood sampling and long waiting times, suggesting that evaluations should be carefully scheduled to minimize disruptions. Efficient medication management, designing welcoming spaces for families, and offering remote monitoring visits are also important to improve the experience children and their families have with the disease and their referring sites and physicians. Aligning clinical visits with school schedules, such as scheduling appointments in the afternoon, can help balance medical care with educational needs, further reducing the burden on families.

2.4. Ideal trial design

The success of a clinical trial is determined not only by the efficacy and safety of the investigational product but also, by the trial design including the selection of appropriate outcome measures. If eligibility criteria are not aligned with the pharmacological characteristics of the study drug, or if the primary endpoint lacks sensitivity to detect change within the trial's timeframe, the trial may fail to demonstrate efficacy, potentially resulting in the premature discontinuation of the investigational product. Therefore, careful consideration of the target population and outcome measures is essential, particularly in pediatric trials for rare diseases such as DM1. Patient selection must depend on the mechanism of action, delivery route, pharmacodynamic and kinetic properties of the drug along with a range of additional considerations beyond safety. In this context, longitudinal natural history data are important for identifying disease phases when a child is naturally improving as such periods may confound the interpretation of treatment effects by potentially masking the true efficacy of the investigational drug. Ideally the investigational product would be most appropriate in periods characterized by clinical stability or deterioration so that any potential benefit observed can be most likely be ascribed to the investigational product and not to the natural course of the disease. This implies having a large amount of data from natural history studies on the progression of disease in its different aspects.

In pediatric DM1, the clinical presentations are predominately characterized by cognitive and behavioral impairments rather than by neuromotor deficits compared to adult-onset presentations. This highlights the need for reliable and sensitive outcomes measures focused on CNS function. Consensus among workshop participants emphasized the need for additional comprehensive natural history data in pediatric populations. In particular, additional data are required CNS biomarkers, brain imaging findings, and splicing profiles to better provide indications for trial design and endpoint selection. The identification of existing gaps, lessons learned from ongoing observational studies and the single pharmaceutical trial conducted thus far in the pediatric DM1 population, stimulated a discussion on practical recommendations for design and implementation of clinical trials in children with DM1. These elements are summarized in a practical checklist developed during the workshop. Given the substantial disease burden in children with congenital and childhood-onset DM1 and its impact on families, there is a strong imperative to ensure that this population is not excluded from therapeutic advances. With appropriate trial design and implementation strategies, inclusion of pediatric patients in ongoing and future clinical trials is both feasible and necessary—and should be pursued sooner rather than later.

2.5. Future and ongoing projects

There were several take-home messages from the workshop. A central conclusion was the pressing need to strengthen collaborative efforts across existing research networks and ongoing observational studies. This implies adopting the procedures and tests discussed during the workshop with careful considerations of the mandatory and 'nice to have' tasks established through group consensus. Follow-up discussions and data collection will provide evidence of the level of implementation and advances in the field. More specifically, the comparison between the adult and pediatric phenotypes prompted discussion on the pathophysiological mechanisms involved and how applicable these can be to both adults and pediatric populations.

The distribution of the RNA foci across various regions of the brain (neuronal and non-neuronal) and in specific areas highlights the need for a deeper understanding of disease pathomechanisms beyond altered splicing and DMPK involvement. More specifically the role of the foci within the cerebellar nuclei may trigger additional investigation regarding the potential contribution of cerebellar dysfunction to cognitive impairment in DM1. Furthermore, to understand to the extent the neurodevelopmental and neurodegenerative processes overlap in DM1 additional longitudinal natural history data are needed on neuropsychological, linguistic, neuroimaging and clinical manifestations across developmental stages. The implementation of brain MRI to investigate CNS involvement in the pediatric presentations of DM1 was discussed and endorsed by the workshop participants. The extent to which MRI findings will enhance understanding of disease pathophysiology remains to be determined and will depend on the systematic acquisition and analysis of imaging data. It was further agreed that a comprehensive review of the existing literature, particularly MRI studies involving children with severe disability and multisystem involvement, would be helpful in the development of standardized MRI protocols, including guidelines for anesthetic procedures. The preclinical discussions and the splicing profiles available from the observational studies strongly supported the need for biomarkers that can hopefully align to the pattern of progression of clinical and cognitive findings.

Ongoing exploratory studies are essential before reaching a consensus on specific biomarkers suitable for collection across multiple sites. Natural history data collected through established clinical research networks are expected to provide results from a relatively pediatric large cohort within the next 2 years. These results will provide the framework for determining the most appropriate outcome measures to be considered in future clinical trials including optimal age groups and observation periods. Clinical trial readiness will largely depend on the trial adherence and implementation of the points recommended during the workshop but also on the patients, advocacy representatives, families and pharmaceutical companies supporting the networks facilitating collaboration and educational support.

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Industry and Regulatory Representatives

The workshop was attended by representatives from the pharmaceutical industry, including Sanofi S.A. (France) and Dyne Therapeutics (USA), who contributed their perspectives on regulatory frameworks, industry development strategies, and potential avenues for collaboration in future clinical and translational research initiatives.

The European Medicines Agency (EMA) participated in the workshop with the objectives of providing valuable expertise on regulatory guidelines for drug development, clinical trial design, and safety requirements.

Patient representatives

Marco Codegoni and Davide Sala, accompanied by his wife Cristina Motton, from Italy; Jorg Van Gent from the Myotonic Dystrophy Foundation and Bas Haasakker, Vice President of Euro-DyMA (European Dystrophia Myotonica Association), from the Netherlands.

Funding

This workshop was supported by Arthex Biotech, Dyne Therapeutics and Sanofi.

CRediT authorship contribution statement

Susanna Pozzi: Writing – original draft. **Dirk J.J. Sweere:** Writing – original draft. **Federica Trucco:** Writing – original draft. **Nicholas E. Johnson:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization. **Valeria A. Sansone:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Valeria A. Sansone participates in Advisory Boards or Teaching activities for Biogen, Roche, Avexis, PTC, Santhera, Sarepta, Dyne

Nicholas E. Johnson has received grant funding from NINDS (R01NS104010, U01NS124974) and the FDA (7R01FD006071). He receives royalties from the CCMDHI and the CMTHI. He receives research funds from Novartis, Takeda, PepGen, Sanofi Genzyme, Dyne, Vertex Pharmaceuticals, Fulcrum Therapeutics, AskBio, ML Bio, and Sarepta. He has provided consultation for Arthex, Angle Therapeutics, Juvena, Rgenta, PepGen, AMO Pharma, Takeda, Design, Dyne, AskBio, Avidity, and Vertex Pharmaceuticals. He has equity in Repeat RNA Therapuetics, Angle Therapeutics, Evolyra Therapeutics, and Juvena Therapeutics.

Susanna Pozzi: none

Dirk J.J. Sweere: none

Federica Trucco reports participation in Scientific Advisory Boards for Roche UK and Italy and teaching initiatives for Biogen, Avexis, Roche, and BREAS.

Acknowledgements

The workshops and next generation programme are made possible thanks to the financial support of the European Neuromuscular Centre (ENMC) and its Full Partners: Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Muscular Dystrophy Campaign (UK), Muskelsvindfonden (Denmark), Prinses Beatrix Spierfonds (The Netherlands), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Spierziekten Nederland (The Netherlands), Telethon Foundation (Italy). In addition, we would like to thank the Associated Partners: Österreichische Muskelforschung (Austria), SMA Europe, TREAT-NMD, World Duchenne Organisation, World Muscle Society (WMS), and the members of the ENMC Company Forum: Amicus Therapeutics, Dyne Therapeutics, Lupin Neuroscience, Novartis, Roche, Sanofi, Santhera and Sarepta. We wish to thank the ENMC for their invaluable support in the organization of the workshop. We are deeply grateful to the patient representatives and families, who are active partners in the care pathway and essential voices both in clinical practice and research. In particular, we acknowledge the important contribution of Euro-DyMA (European Dystrophia Myotonica Association) and its representatives. We also acknowledge the European Medicines Agency (EMA) for its participation and contribution, as well as the industry and regulatory representatives from Sanofi (France) and Dyne Therapeutics (USA) for their collaborative engagement in this initiative.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2025.106252.

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