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Authors

Rezende, Lorena V
Ortega, Adriana B
Do Valle, Daniel A
et al.

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CASE SERIES

Autism spectrum disorder in children with spinal muscular atrophy type 1: Case series

Lorena V. Rezende[1,2] | **Adriana B. Ortega**[2] | **Daniel A. Do Valle**[1,2] | **Tiago S. Bara**[1,3] | **Mara L. Cordeiro**[1,3,4]

[1]Faculdades Pequeno Principe, Curitiba, PR, Brazil

[2]Hospital Pequeno Príncipe, Curitiba, PR, Brazil

[3]Instituto de Pesquisa Pelé Pequeno Principe, Curitiba, PR, Brazil

[4]Department of Psychiatry and Biobehavioural Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Correspondence
Mara L. Cordeiro, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, 10833 Le Conte Ave, Los Angeles, CA 90095, USA.
Email: mcordeiro@mednet.ucla.edu

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Abstract

This case series provides a detailed description of the coexistence of spinal muscular atrophy (SMA) type 1 and autism spectrum disorder (ASD) in children treated with disease-modifying therapies. Among 13 patients (2–7 years; mean age 4 years [SD 2 years], eight males), five met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision criteria for ASD—a proportion substantially higher than expected and exceeding recent reports in SMA cohorts. These findings indicate that ASD may be underrecognized in this population and that traditional screening tools, such as the autism trait assessment, may fail to detect symptoms because of the severe motor and communicative limitations characteristic of SMA. Although all children demonstrated meaningful motor gains after treatment, those with SMA and ASD showed marked cognitive and adaptive impairments, particularly in communication, socialization, and daily living skills. The dissociation between motor improvement and neurodevelopmental outcomes underscores the need for tailored assessments and continuous behavioral surveillance. This report provides clinically relevant insights and highlights the importance of adapted diagnostic approaches for neurodevelopmental evaluation in SMA.

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by social-communication impairments and restricted, repetitive behaviors, arising from complex neurogenetic and environmental interactions.[1] Although historically regarded as unrelated conditions, emerging evidence suggests that children with spinal muscular atrophy (SMA)—a severe neuromuscular disorder caused by *SMN1* mutations—may exhibit cognitive, communicative, or behavioral difficulties that resemble ASD.[2–4] These observations challenge long-standing assumptions that cognition is fully preserved in SMA and raise important diagnostic considerations, particularly in the era of disease-modifying therapies that have transformed survival and developmental trajectories.

With improved motor and respiratory outcomes after treatments such as nusinersen, risdiplam, and gene therapy, children with SMA type 1 now survive long enough for more complex neurodevelopmental profiles to emerge. Severe motor limitations, impaired expressive communication, and medical fragility frequently complicate ASD assessment, increasing the risk of diagnostic overshadowing.

This case series describes children with SMA type 1 who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria for ASD.[1]

Abbreviations: ASD, autism spectrum disorder; SMA, spinal muscular atrophy; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

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It examines the associated developmental profiles, emphasizing the clinical relevance of this emerging association and the need for integrated, longitudinal neurodevelopmental surveillance to guide long-term care.

CASE PRESENTATIONS

Participants

Thirteen children with SMA type 1 were included in the study. They were 2 to 7 years old (mean 4 years SD 2 years), and eight were male. All included children had a homozygous *SMN1* deletion with two copies of *SMN2* and were receiving disease-modifying therapy.

Five of the thirteen children met DSM-5-TR diagnostic criteria for ASD. Table 1 summarizes clinical and demographic characteristics..

Ethics

The study was approved by the Institutional Ethics Committee at Hospital Pequeno Príncipe (CAAE 67299923.0.0000.0097) and conducted in accordance with national research guidelines (CEP/CONEP). Written informed consent was obtained from the legal guardians of all participants.

Diagnostic assessment

ASD diagnoses were established by an experienced multidisciplinary team comprising neuropediatricians, neuropsychologists, and a neuroscientist. Diagnostic determinations integrated developmental history, direct clinical observation, adaptive functioning, and comprehensive neuropsychological assessment. The autism trait assessment was administered as an additional screening measure; however, it did not influence the final diagnostic decision, which was based on DSM-5-TR criteria. Table 2 presents the full data set for the sample, including age, sex, Snijders-Oomen Nonverbal Intelligence Test (for ages 2 years 6 months–7 years) scores, Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) non-motor domains, Child Behavior Checklist profiles, and autism trait assessment results..

Behavioral findings

Behavioral assessment using the Child Behavior Checklist indicated the presence of internalizing symptoms in a subset of participants, without a pattern specific to ASD. Autism trait screening outcomes also varied across the sample, with both positive and negative results observed across individuals. All behavioral data are presented descriptively, without inferential statistical analyses.

What this paper adds

- Five of the 13 children with spinal muscular atrophy type 1 had autism spectrum disorder.
- Consistent patterns of significant adaptive functioning impairments across the cohort were identified.
- There was a dissociation between motor improvement after disease-modifying therapies and cognitive-adaptive developmental progress.

Regarding cognitive functioning, mean Non-verbal IQ scores showed a tendency toward lower performance among participants with ASD compared to those without ASD, although substantial variability was observed within both groups.

Cognitive findings

Descriptive analysis of nonverbal cognitive functioning revealed lower mean Snijders-Oomen Nonverbal Intelligence Test scores among children with SMA and co-occurring ASD compared to those with SMA only. Considerable variability was observed within both groups, and no inferential statistical analyses were performed.

TIMELINE OF TREATMENT INITIATION AND NON-VERBAL IQ SCORES

Figure 1 depicts individual ages at treatment initiation alongside Snijders-Oomen Nonverbal Intelligence Test Non-verbal IQ outcomes. An inverse relationship emerged, with earlier treatment initiation associated with more favorable IQ scores, while delayed initiation corresponded to reduced cognitive performance. All children with ASD fell within the later-treatment range, indicating a potential window of heightened neurodevelopmental risk when therapy is started after the onset of early social-communication symptoms..

Adaptive functioning

Descriptive analysis of adaptive functioning based on the Vineland-3, indicated lower mean scores across all assessed non-motor domains among children with ASD compared to those without ASD. The health and motor skills domain was not included in group descriptions because it was administered to only a subset of participants (three children with ASD and five without ASD) and because motor impairments inherent to spinal muscular atrophy would confound interpretation, in accordance with Vineland-3 guidelines.

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Individual case summaries

The full data set for the five children diagnosed with ASD is detailed in Table 3. Concise clinical summaries for each case are described below..

Patient 2: Early treatment initiation; high dependence in daily activities; severely limited communication; ventilatory support required. ASD diagnosis confirmed.

Patient 5: History of global developmental delay and clinical instability; marked cognitive and adaptive limitations; extensive care needs. ASD diagnosis associated with global developmental delay.

Patient 6: Clinical course characterized by respiratory complications and loss of previously acquired motor abilities; minimal communication; complete care dependence; reduced adaptive functioning. ASD diagnosis confirmed.

Patient 7: Significant cognitive impairment; reduced autonomy; limited social participation; broad communication and functional limitations. ASD diagnosis confirmed.

TABLE 1 Demographic characteristics of the study cohort ($n = 13$).

Characteristic	Value
Age, mean (SD)	4 years (2 years)
Sex (male/female)	8/5
Genetic profile	*SMN1* deletion, 2 *SMN2* copies (all patients)
Therapy	Zolgensma ($n = 12$)
	Nusinersen ($n = 13$)
	Risdiplam ($n = 2$)[a]

[a]Some children received more than one therapy.

Patient 8: Global developmental delay; absence of oral language; substantial adaptive deficits requiring extensive support. ASD diagnosis associated with global developmental delay.

Integrated summary of findings

ASD was identified in five of the 13 participants. Internalizing symptoms were present across the sample but were not specifically associated with ASD. Children with ASD showed lower mean Non-verbal IQ scores and more pronounced adaptive limitations. The co-occurrence of SMA and ASD reflects increased clinical complexity and broader neurodevelopmental variability, underscoring the need for longitudinal neurobehavioral monitoring.

DISCUSSION

This case series highlights the clinical relevance of identifying features of autism spectrum disorder (ASD) in children with spinal muscular atrophy (SMA) type 1, an association that has been increasingly recognized but remains underexplored. Emerging reports have described the co-occurrence of ASD features in children with SMA, although prevalence estimates remain variable and methodological challenges persist.[4,5]

Of the 13 participants, five met DSM-5-TR diagnostic criteria for ASD, a proportion higher than rates reported in recent treated SMA cohorts and well above general population estimates. Variability across studies may reflect

TABLE 2 Neuropsychological assessment scores for the study cohort.

		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13
Sex		F	**M**	F	F	**M**	**M**	**M**	**F**	F	F	F	M	F
Age (years)		2	**2**	2	3	**4**	**3**	**6**	**2**	4	4	5	5	7
SON-R	EE	111	**73**	78	75	**54**	**78**	**52**	**75**	73	94	73	86	83
	ER	117	**91**	94	97	**65**	**97**	**52**	**83**	91	111	91	123	75
	IQ	115	**80**	85	85	**56**	**86**	**50**	**77**	80	103	80	104	62
Child Behavior Checklist	IN	29	**59**	53	43	**47**	**47**	**51**	**56**	60	37	58	43	46
	EX	28	**52**	39	44	**44**	**32**	**50**	**48**	42	40	56	40	49
	TOTAL	28	**57**	46	41	**45**	**41**	**48**	**51**	51	36	54	43	47
Vineland-3	COM	101	**20**	83	79	**51**	**61**	**36**	**55**	83	89	49	76	72
	ADL	81	**27**	86	61	**50**	**54**	**38**	**66**	75	84	68	62	54
	SOC	88	**33**	96	90	**62**	**69**	**63**	**64**	81	86	62	85	79
	CCA	87	**29**	86	74	**57**	**62**	**50**	**62**	77	84	61	72	67
	HMOT	-	-	-	50	**41**	**48**	**28**	-	4	57	47	52	-
ATA	Total	0	**16**	6	4	**13**	**18**	**24**	**6**	8	2	9	2	4

Notes: ATA scores ≥15 were considered positive. A negative ATA result does not exclude ASD, which was determined through multidisciplinary clinical assessment. Motor function was assessed using the CHOP INTEND scale. Bold type indicates diagnosis of ASD.

Abbreviations: ADL, activities of daily living; ASD, autism spectrum disorder; ATA, autism trait assessment; CCA, community and citizenship activities; CHOP INTEND, Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders; COM, communication; EE, executive scales; ER, reasoning scales; EX, externalizing; F, female; HMOT, health and motor skills; IN, internalizing; M, male; SOC, socialization; SON-R, Snijders-Oomen Nonverbal Intelligence Test; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

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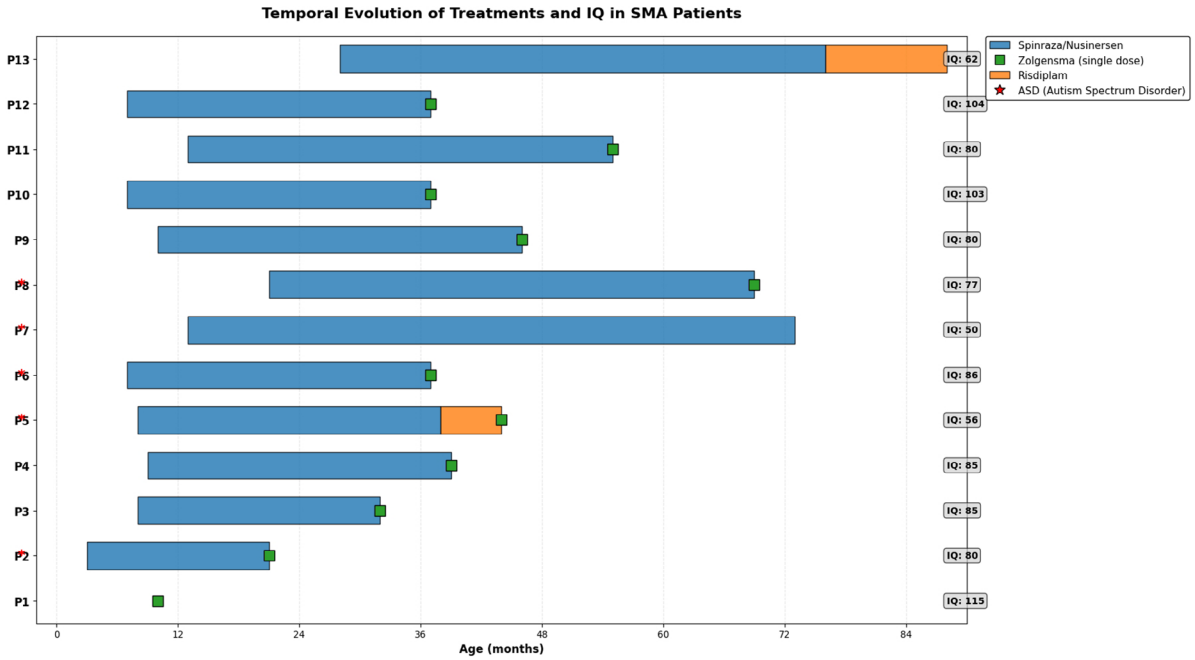

FIGURE 1 Timing of disease-modifying treatment initiation in relation to individual Non-verbal IQ scores.

methodological differences, including the limited sensitivity of screening tools in children with severe motor impairment. Broader investigations of cognition and communication in SMA have further highlighted heterogeneous neurodevelopmental profiles, including impairments in nonverbal reasoning, language, and executive functioning.[6–9]

In this sample, only three of the children with ASD screened positive on the autism trait assessment, underscoring concerns raised in previous work that commonly used ASD measures may not adequately capture autistic behaviors in non-ambulant or minimally verbal SMA populations. Criterion-standard assessments such as the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview–Revised also rely heavily on motor and communicative behaviors that may be unfeasible for many children with SMA type 1, necessitating adapted protocols and careful integration of developmental history and clinical judgment.

Cognitive assessment using the Snijders-Oomen Nonverbal Intelligence Test indicated borderline overall performance with wide interindividual variability, and lower scores among children with SMA and co-occurring ASD. Previous studies have reported that severe muscle weakness, bulbar dysfunction, reduced opportunities for exploration, and fatigue may negatively influence cognitive development in SMA.[2,7,10] These factors can affect the acquisition of visuomotor integration, nonverbal reasoning, and executive processes—domains targeted by the Snijders-Oomen Nonverbal Intelligence Test. The more pronounced impairments observed in the SMA and ASD subgroup suggest a combined contribution of motor limitations, SMA-related biological factors, and ASD-associated neurocognitive characteristics. This interaction may manifest as difficulties in problem-solving, learning, and social engagement.

Adaptive functioning, assessed using the Vineland-3, showed marked impairments in communication, socialization, and daily living skills, consistent with previous descriptions of significant functional limitations in SMA type 1. Children with SMA and ASD demonstrated even lower scores, suggesting that adaptive outcomes reflect both neuromuscular constraints and core ASD features. Limited mobility, reduced participation in social contexts, and chronic complex developmental disability may restrict opportunities for developing autonomy and social-communication skills. Prior work has suggested that expressive language limitations inherent to SMA type 1 may further compound ASD-related communication difficulties.

Behavioral profiles derived from the Child Behavior Checklist demonstrated a predominance of internalizing symptoms, particularly anxiety, a pattern described in other chronic neuromuscular conditions. These symptoms may relate to restricted autonomy, coping challenges, and the psychosocial impact of chronic illness. Externalizing difficulties were less frequent, in line with patterns reported in children with substantial physical limitations. Notably, a divergence emerged between motor gains—often substantial after disease-modifying therapies—and cognitive-adaptive outcomes, which were comparatively limited. This dissociation aligns with recent findings suggesting that motor and neuropsychological development may follow partially independent trajectories in SMA. Earlier treatment initiation, ideally presymptomatic, appears to support more favorable neurodevelopmental outcomes, although improvements remain heterogeneous.[3,11,12]

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TABLE 3 Clinical and neuropsychological characteristics of the five patients diagnosed with ASD.

	Case ID	P2	P5	P6	P7	P8
Sex		M	M	M	M	F
Age (years)		2	4	3	6	2
Age (months) at start of treatment	**Nusinersen**	3	8	7	15	6
	Risdiplam	-	16	-	-	-
	Zolgensma	19	43	13	-	10
	Before medication	12	18	32	18	13
CHOP INTEND	**After medication**	46	26	38	58	28
	Maximum motor frame	Sit with lateral support	Sit with support	Sit with support	Standing with support and orthosis	Sit with cervical support
SON-R	**EE**	73	54	78	52	75
	ER	91	65	97	52	83
	IQ	80	56	86	50	77
Child Behavior Checklist	**IN**	59	47	47	51	56
	EX	52	44	32	50	48
	Total	57	45	41	48	51
Vineland-3	**COM**	20	51	61	36	55
	ADL	27	50	54	38	66
	SOC	33	62	69	63	64
	CCA	29	57	62	50	62
	HMOT	-	41	48	28	-
ATA	**Total**	16	13	18	24	6
Diagnosis	-	ASD	GDD + ASD	ASD	ASD + ID	GDD + ASD

Notes: ATA scores ≥15 were considered positive. A negative ATA result does not exclude ASD, which was determined through multidisciplinary clinical assessment. Motor function was assessed using the CHOP INTEND scale.

Abbreviations: ADL, activities of daily living; ASD, autism spectrum disorder; ATA, autism trait assessment; CCA, community and citizenship activities; CHOP INTEND, Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders; COM, communication; EE, executive scales; ER, reasoning scales; EX, externalizing; F, female; GDD, global developmental delay; HMOT, health and motor skills; ID, intellectual disability; IN, internalizing; M, male; SOC, socialization; SON-R, Snijders-Oomen Nonverbal Intelligence Test; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

Strengths of this case series include detailed neuropsychological characterization, multidisciplinary assessment, and the use of adapted behavioral diagnostic procedures suitable for children with severe motor impairment. Limitations include the small sample size, inherent to the low prevalence of SMA type 1, and heterogeneity in treatment timing and clinical presentation. The absence of Autism Diagnostic Observation Schedule and Autism Diagnostic Interview–Revised administration is a methodological limitation, though justified by motor constraints; nevertheless, the integration of developmental history, standardized measures, and expert clinical judgment supports diagnostic confidence.

In summary, ASD can occur in children with SMA type 1 and is associated with additional cognitive and adaptive challenges, irrespective of motor improvements achieved with disease-modifying therapies. These findings emphasize the need for ongoing neurobehavioral monitoring, routine neuropsychological evaluation, and diagnostic approaches adapted to motor limitations.[13] By documenting this association, the study contributes to a deeper understanding of the interplay between SMA and ASD and underscores the importance of future research exploring underlying neurobiological mechanisms, developmental trajectories, and targeted interventions for this population.

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The authors declare that they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Deidentified data supporting the findings of this study are available from the corresponding author, Mara Cordeiro, upon reasonable request and completion of a data transfer agreement. Genetic data have been deposited in ClinVar.

ORCID

Daniel A. Do Valle https://orcid.org/0000-0001-9005-6726
Mara L. Cordeiro https://orcid.org/0000-0002-0235-8001

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