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(RESEARCH ARTICLE)

Outcome of Pediatric Rehabilitation in SMA post gene therapy

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder marked by the degeneration of alpha motor neurons in the spinal cord, leading to progressive proximal muscle atrophy and paralysis. The incidence of SMA is notably higher in the Middle East compared to the Western world, partly due to the higher rates of consanguineous marriages in the region. Recent advances have introduced therapies such as Spinraza, Zolgensma, and Risdiplam which have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These treatments represent a significant shift from managing progressive neurodegeneration to achieving milder, chronic forms of the disease.

The introduction of gene therapy has transformed SMA management, necessitating a comprehensive, multidisciplinary approach. This approach involves collaboration among healthcare professionals including pediatricians, neurologists, physical medicine specialists, pulmonologists, and rehabilitation experts, as well as therapists such as physical, occupational, and speech therapists and dietitians, with involving patients, caregivers, and families.

This paper explores the role of rehabilitation in optimizing outcomes for pediatric SMA patients receiving gene therapy at Qatar Rehabilitation Institute. It aims to evaluate how early and comprehensive rehabilitation strategies can enhance the effectiveness of expensive interventions like gene therapy.

A multidisciplinary team whose follow the standard of care (practice guidelines for clinical care 2007-2018) at the Qatar Rehabilitation Institute provides long-term rehabilitation , integrated medical care for SMA patients post-gene therapy. This care includes positioning and bracing, supported standing, stretching, management of musculoskeletal deformities, physical exercise training (including aerobics, hydrotherapy and strengthening exercises), use of assistive devices, speech and dysphagia treatment. The study assesses the impact of these rehabilitation strategies on motor function, daily living activities, and overall quality of life.

Rehabilitation play important role in improving motor function and daily performance like range of motion in SMA patients undergoing gene therapy. Early intervention and ongoing rehabilitation have contributed to better outcomes in terms of motor skills, activities of daily living, and quality of life.

The shift to gene therapy necessitates an evolved approach to SMA management. Effective rehabilitation is crucial in maximizing the benefits of such costly treatments.

This paper Describe improvement of SMA with intensive pediatric rehabilitation who received therapeutic intervention (gene therapy with or without Nusinersin) in pediatric rehabilitation department in Qatar by monitoring in the score of CHOP INTENT tools / Hammersmith.

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This study is a retrospective observational study where data will be collected for about 18 children with SMA between age 0 to 14 years from period 01/06/2018 to 31/08/2024 who are followed up in SMA multidisciplinary clinic , Qatar Rehabilitation Institute.

Keywords: Spinal muscular atrophy; Pediatric Rehabilitation; Gene therapy

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis. Estimated incidence is 1 in 6,000 to 1 in 10,000 live births and carrier frequency of 1/40-1/60. .(1) This disease is characterized by generalized muscle weakness and atrophy predominating in proximal limb muscles, and phenotype is classified internationally into four grades of severity (SMA I, SMAII, SMAIII, SMA IV) based on age of onset and motor function achieved or new classification of non sitter, sitter or walker particularly in the Middle East where the incidence has been predicted to range between 10 and 193 in 100,000 live births, almost 40-fold higher than in Western populations8 . However, there is a lack of data to accurately estimate SMA epidemiology across Arab populations (2)

SMA incidence of up to 40-fold higher than the Western world is potentially a result of the increased rate of consanguineous marriages in the region. Consanguinity was reported in 45.5% of SMA patients in Egypt. Globally, carrier frequency has been estimated to range between 1 in 45 and 1 in 100 people. The carrier frequency in the region, however, is thought to be much higher, with 1 in 20 normal individuals unrelated to SMA patients being carriers (3)

SMA treatments, Spinraza 2016 and Zolgensma 2019, Risdiplam 2020 have been approved for marketing by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) within the last few years ,these therapies were extensively tested in pre-clinical experiments before progressing to clinical trials.(4)

Drugs that increase levels of survival motor neuron (SMN) protein are revolutionizing the disease course and treatment of spinal muscular atrophy (SMA) across the spectrum of the disease.

Clinical responses in patients with symptomatic SMA can reach levels that were unanticipated, but the longer the disease duration and the greater the severity, the more modest the response. (5)

Zolgensma is gene replacement of the mutated SMN1 with normal SMN1. Onasemnogene abeparvovec is an adeno-associated viral vector-based gene therapy drug that replaces the function of the missing or non-functioning SMN1 gene into the patient's cells. It is a once-only treatment given by an intravenous infusion over 60 min. In May 2019, it became the first gene therapy drug for SMA to be approved by the USFDA. Onasemnogene abeparvovec is indicated for the treatment of children

Zolgensema is reportedly the most expensive drug in the world, costing $2.125 million Dollar for a single injection.

Other treatments are also costly, with nusinersen costing $118,000 per vial and about $708,000 for the first year of treatment. (7)

An early diagnosis is important since in SMA type 1, 90% of alpha motor neurons, are lost by six months of age. As such, some authors advocate for prenatal diagnosis.

A multidisciplinary approach to evaluation and management includes a strong partnership between physicians (pediatrics rehabilitation, neurology, genetic, and Pulmonology), therapists (physical therapy, occupation therapy, speech therapy and dietitian), patients, caregivers and families

There are multiple tools to monitor the functional impairment and progress. It is important to obtain training in the use of these scales to know how to rate each item. The choice of the scale should take into account the type of SMA, the age of the patient, the expected changes and the items evaluated on each scale.

The main objectives of rehabilitation start with non sitter or sitters to optimize the function and minimize the impairment, optimize the tolerance to various potion by doing primary and functional assessment. The main objectives for rehabilitation in walkers , sitter and non sitter to promote function, improve mobility, balance and endurance. In all patients, determining appropriate mobility aids, adaptive equipment, assistive technology and environmental adaptations will allow the achievement of the highest independence level(6)

This paper is describing the rule of rehabilitation performed in patient with SMA who received gene therapy to optimize the outcome of such expensive intervention.

Objectives

Goal of Study:

Primary objective:

- -Describe improvement of SMA cases who received therapeutic intervention (gene therapy with or without Nusinersin) and intensive rehabilitation in pediatric rehabilitation section in Qatar Rehabilitation Institute by monitoring the increasing in the score of CHOP INTENT tools / Hammersmith.
- -Improve or maintain the functional level using CHOP INTENT and Hammersmith, requiring patient and family education, pain management, exercise, and posture modification.

Secondary objective :

- To explain the scoliosis stability or improvement: By checking cobb angle in x ray for contraction and hip dislocation.
- To sum up the swallowing improvement: By shifting from non oral to oral feeding
- improvement in Activities of Daily Living (ADL): To be more independent in tasks like dressing, bathing, and hair combing
- To lay out how the nutritional status has improved :by catch up growth percentile for weight and height as per WHO and CDC
- Explore any possible association between demographic and comorbidity with effect on CHOP INTENT and Hammersmith score.
- To provide insights into the effectiveness of a multidisciplinary approach for treating pediatric SMA patients post-gene therapy, helping to inform future therapeutic strategies and improve patient outcomes.

Indicate if this is a retrospective data review

0 Retrospective Chart/data Review (Retrospective means the data is already in existence when the project is submitted to the IRB).

Provide the date range of the chart review (if this is a retrospective chart review, the end date must come before the submission date): 01/06/2018 to 31/08/2024, no follow up data will be collected

2. Study Methodology

This study is retrospective observational study where data will be collected for about 18 children with SMA 14 patients type 1 and 4 patients type 2 age between 0 to 14 years from period 01/06/2018 to 31/08/2024 who are followed up in pediatric rehabilitation clinic, Qatar Rehabilitation Institute

2.1. Data Collection

Data will be collected from the electronic medical records (Cerner) of the Pediatric Rehabilitation Department.

2.2. Topographic Classification

Participants will be classified according to their SMA type, focusing on different topographic classifications to tailor therapy strategies.

The interdisciplinary team for children with SMA post-gene therapy includes the rehabilitation physician to oversee the overall care plan, physiotherapists to enhance mobility and strength, occupational therapists to support daily living skills, speech therapists to address communication and swallowing issues, respiratory therapists to manage respiratory health, and dietitians to ensure proper nutrition and growth.

The rehabilitation strategy for children with SMA post-gene therapy should be dynamic, personalized, and focused on promoting functional independence. Regular follow-ups and a supportive environment are essential for maximizing therapeutic benefits and improving quality of life.

2.3. Study Population and Study Setting/ Location

2.3.1. Study Population

This study included all patient with SMA whose received Gene therapy and intensive rehabilitation programs.

2.3.2. Inclusion criteria

Patients with diagnosis of SMA type 1 and type 2 who receive gene therapy with or without Spinraza and Risdiplam age 0 to 14 years, who are followed up in pediatric rehabilitation SMA multidisciplinary clinic, Qatar Rehabilitation Institute

2.3.3. Exclusion criteria

Patients with SMA who are under mechanical ventilation.

Patients with genetic or neurological deficit other than SMA like congenital muscular dystrophy or Duchenne muscular dystrophy.

2.3.4. Syndromic patients

Study procedures

Patients are attending clinic in pediatric rehabilitation SMA multidisciplinary clinic, After the patient meets with the team, which consists of a physician, physiotherapist, occupational therapist, speech and language therapist, and dietitian, the primary assessment and functional assessment are completed. Patients have examinations and assessments to score in the CHOP INTENT/Hammersmith tools.

Every team member will input their results into the common Excel document. To examine data from both pre- and post-rehabilitation.

2.4. Study Duration and Timelines

Table 1 Study timeline and project activities

Task	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Getting final approval of the project	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study design		**X**										
Data collection			**X**	**X**	**X**							
Data analysis					**X**	**X**						
Writing up							**X**	**X**	**X**			
Progress report						**X**						
Final report												**X**

2.5. Informed Consent

This is a retrospective study, and subjects will not be recruited in this study, hence informed consent will not be needed.

2.6. Subject Withdrawal/ Withdrawal of Consent

Adverse Event Reporting

No adverse events are expected

2.7. Risk

No risk

2.8. Bio-Specimens & Sample Collection

- None
- Admission, transfer, discharge
- Its for Outpatient pediatric rehabilitation case

2.9. Outcomes

primary Outcomes:

Describe improvement of SMA cases who received therapeutic intervention (gene therapy with or without Nusinersin) and rehabilitation in pediatric department in Qatar Rehabilitation Institute by increasing in the score of Hammersmith /CHOP INTENT tools

Secondary Outcomes :

- improvement in Activities of Daily Living (ADL): To be more independent in tasks like dressing, bathing, and hair combing
- To sum up the swallowing improvement: By shifting from non oral (NGTor PEG) to oral feeding
- To lay out how the nutritional status has improved :by catch up growth percentile for weight and height as per WHO and CDC
- To explain the scoliosis stability or improvement :By checking cobb angle in x ray

2.10. Data Collection, Management & Confidentiality

Indicate below HOW study data will be collected for the proposed research.

0 Study Forms 1 Study Database 0 Study Web-Based/App 0 Other

Please detail how study data will be coded:

Data will be coded numerically based on each question answered as per data collection sheet

Describe below WHERE and HOW the study data is physically stored.

Data will be collected electronically and fed into Excel data sheet. All the details about the subject will be coded. Data will be collected de identified, cods will be used to cover patient identifier such as Name, HC number, D.O.B. The link between code and identifier will be destroyed once the study finish and de identified data will be stored at least 5 years. Data will be stored in the HMC PI computer after collection of data by research team in pediatric rehabilitation department, QRI.

Describe below WHO controls access to the study data

Principal Investigator

Describe below WHO has access to the study data.

Co-Investigators and the Research team

Describe below HOW the study data is accessed.

The study data will be password protected.

Will subject identifiers be shared outside of HMC? If YES describe below WHOM the study data is shared

No

2.10.1. Study monitoring/Data Safety Monitoring Board (DSMB)

Not applicable

2.11. Statistical Consideration and Data Analysis

Descriptive statistics will be used to summarize and determine the sample characteristics and distribution of the SMA patients. The normally distributed data and results will be presented with mean and standard deviation (SD) with corresponding 95% confidence interval (CI); whereas the median and interquartile range (IQR) will be used for skewed/non-normal data. Categorical data will be summarized using frequencies and percentages. The primary outcome in this current research study is to evaluate and assess improvement and functional level using CHOP INTENT and Hammersmith tools in patients presented with SMA who received therapeutic intervention and intensive rehabilitation. Relationship between CHOP INTENT, Hammersmith and ADL scores will be statistically analyzed using statistical methods Pearson's or Spearman's correlation coefficients. Moreover, associations between categorized scores and other categorical parameters will be examined and assessed using Pearson Chi-square and Fisher Exact tests as appropriate. Quantitative mean scores between the two groups will be statistically compared using unpaired t test or non-parametric Mann Whitney U test as appropriate. Univariate and multivariate Linear regression (using actual score values of CHOP INTENT, Hammersmith, and ADL scores) and logistic regression analysis (using categorical outcome variables following categorization of scores using arbitrary/standard cutoff scores applicable) will be performed to explore and assess impact of potential factors and predictors for primary outcome measures. Secondary objectives (which includes to evaluate the scoliosis improvement or stability and improvement in swallowing and ADL and to explore any possible association between demographic, comorbidities and CHOP INTENT and Hammersmith scores) will be analyzed using statical methods outlined above. A two-sided P value <0.05 will be considered as statistically significant. All statistical analyses will be done using statistical packages SPSS version 29.0 (Armonk, NY: IBM Corp).

2.11.1. Adverse Event Reporting

No adverse events are expected

2.12. Ethical Consideration

The study will be conducted in full conformance with principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of MoPH in Qatar.

This study will only be conducted after review and approval from MRC.

2.12.1. Sponsor, Funding & Collaborator Information

No funding will be requested

2.12.2. Dissemination of Results and Publication policy

After completion of this study, it will be published but the journal is not yet specified. Once the study is completed, the manuscripts will be prepared and submitted for publication in peer-reviewed journal. Also, the finding of the study will be shared at appropriate professional conferences or symposia.

3. Result

Table 2 Baseline characteristics of the study participant

Parameters	**Frequency (%)**
	n=19
Demographics: Age (years)	median 5 (IQR 3.9-7)
Gender	
Male	10 (52.6%)
Female	9 (47.4%)
Nationality	
Qatari	9 (47.4%)
Non-Qatari	10 (52.6%)
Clinical:	
Diagnosis	
SMA 1	13 (68.4%)
SMA 2	6 (31.5%)
Age on Diagnosis / Month	median 2 (IQR 2-14)
Age on 1st dose/ month	median 6 (IQR 2-18)
Age on Gene Therapy/ month	median 8 (IQR 5-18)
Ventilation (respiratory support)	3 (15.8%)
Pre-therapy growth (malnourish)	7 (36.8%)
Post-therapy growth (malnourish)	3 (15.8%)
Constipation	5 (26%)
Vomiting and reflexing	3 (15%)
Functional:	
ADL (deficit)	19 (100%)
Strength (deficit)	8 (42.1%)
Fine motor skills (deficit)	10 (47.4%)
Position (deficit)	11 (57.9%)
Play skill (deficit)	2 (10.5%)
Scoliosis (deficit)	8 (42.1%)
Mode of feeding (tube feed)	5 (26.3%)
Secretion management (deficit)	14 (73.7%)
Mandibular range of motion/strength (weak)	5 (26.3%)
prolonged Feeding time (deficit)	5 (26.3%)
Poor Chewing skills (deficit)	3 (15.8 %)
Speech Difficulties (deficit)	11 (57.8%)

Activity Limitation score (severe)	6 (31.6%)
IQR: Inter-quartile range	

Children with spinal muscular atrophy (SMA) in this study were mostly diagnosed and treated early, with most having the more severe Type 1. Gene therapy and rehabilitation helped improve nutrition, but many children still had challenges with daily activities and motor skills. Feeding and speech difficulties, scoliosis, and muscle weakness were common, showing that these children need complex, ongoing care.

Table 3 Pre and Post assessment comparison of CHOP-INTEND and Hammersmith scores

Scores	Mean	SD	Mean Difference (95% CI)	P-value
CHOP-INTEND score at pre-assessment	49.11	13.864	8.67 (3.70, 13.64)	0.002
CHOP-INTEND score at post-assessment	57.78	7.550		
Hammersmith score at pre-assessment	34.33	8.829	5.80 (2.21, 9.41)	0.004
Hammersmith score at post-assessment	40.13	11.928		

Both outcome measures showed statistically significant gains, indicating that the therapy improved motor strength and function. Although results varied among individuals, overall motor progress and functional independence increased after treatment.

Motor Function Improvement (CHOP-INTEND): CHOP-INTEND scores increased from 49.11 to 57.78 after therapy (mean difference 8.67, 95% CI 3.70–13.64, p = 0.002), showing a significant boost in gross motor function.

Functional Mobility Enhancement (Hammersmith): Hammersmith scores improved from 34.33 to 40.13 post-therapy (mean difference 5.80, 95% CI 2.21–9.41, p = 0.004), indicating a significant functional gain in seated and mobility tasks.

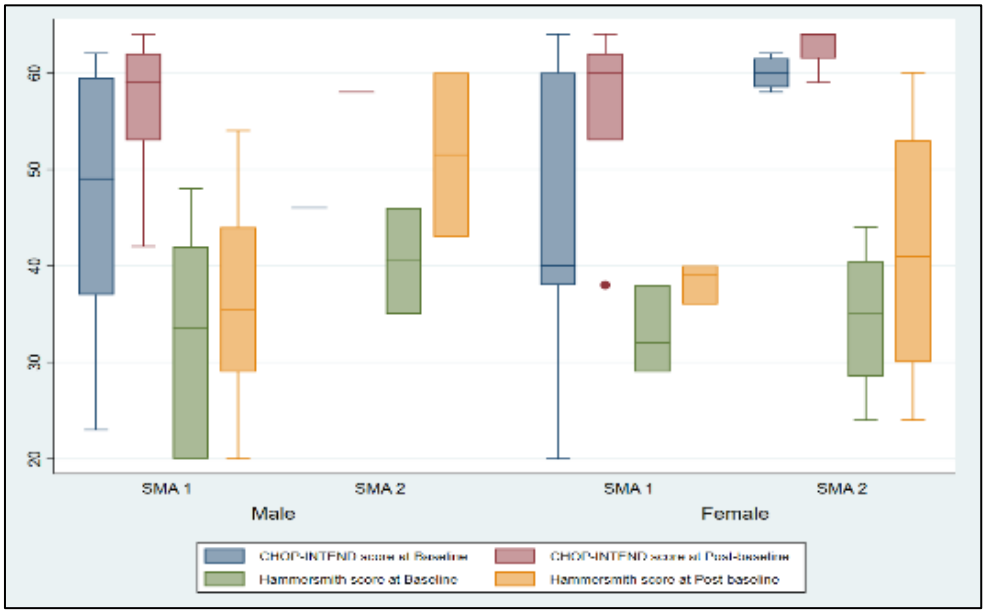

Figure 1 Comparison of SMA type, gender, and rehabilitation intervention tools, including CHOP INTEND and Hammersmith

Table 4 Association between various predictor variables with percentage improvement following gene and Rehabilitation Therapies

		Improvement following Gene and Rehabilitation Therapies	**P-value**
Predictor variables	**Categories**	**Improved, n (%)**	
Gender	Male	8/10(80.0)	0.998
	Female	7/9(77.8)	
Diagnosis			
	SMA 1	10/13(76.9%)	0.997
	SMA 2	5/6(83.3%)	
Ventilation			
	Normal Ventilation	15/16(93.8%)	0.004
	Need Resp. Support	0/3(0%)	
Growth- Pre therapy			
	Normal	10/12(83%)	0.603
	underweight	5/7(71%)	
Growth-post -therapy			
	underweight	2/3(66%)	0.701
	Normal	13/15 (86%)	
	overweight	0/1(0%)	
GI			
	No issue	10/11(90%)	0.347
	Constipation	4/5(80%)	
	Reflex	1/3(33%)	
ADL			
	Deficit	15/19(78.9%)	--
Endurance & Strength			
	Normal	10/11(90%)	0.262
	Deficit	5/8(62.5%)	
Fine motor skills			
	Deficit	7/10(70%)	
Position			
	Normal	8/8 (100%)	0.103
	Deficit	7/11(63%)	
Play skill			
	Normal	13/17(76%)	0.996
	Deficit	2/2(100%)	

Scoliosis			
	Normal	8/11(72%)	0.603
	Deficit	7/8(87%)	
Mode of feeding			
	Oral	12/13(92%)	0.484
	Tube feeding	3/5(60%)	
	Mix of both	0/1(0%)	
Secretion management			
	Yes	12/14(85%)	0.272
	No	3/5(60%)	
Mandibular range of motion/strength			
	Good	12/14(85%)	0.272
	Weak	3/5(60%)	
prolonged Feeding time			
	Yes	3/5(60%)	0.410
	No	9/9 (100%)	
	NA	3/5(60%)	
Poor Chewing skills			
	Yes	1/3(33%)	0.210
	No	10/10(100%)	
	NA	4/6(66.7%)	
Speech Difficulties			
	Yes	8/11(72%)	0.954
	No	5/6(83%)	
	NA	2/2(100%)	
Activity Limitation score			
	Sever	4/6 (66%)	0.509
	Moderate	3/5(60%)	
	No impairment	8/8(100%)	

Ventilation status was the only significant predictor of improvement after gene and rehab therapy ($p = 0.004$); participants with normal respiratory function showed greater progress. No statistically significant differences were found by gender, SMA type, or nutritional status, though positive clinical trends appeared in those with better baseline motor, feeding, and positional control. These results suggest that respiratory capacity is important for therapy responsiveness, and other factors may warrant further study.

Table 4 A Effect of various potential predictors and covariates on outcome variable percentage change from pre-assessment CHOP-INTEND score

Predictor variables	Regression coefficient (β)	Std. Error (SE)	t-value	P-value	95% Confidence Interval for (β)		Partial Eta Squared
					Lower Bound	Upper Bound	
Gender: Male	-32.605	25.112	-1.298	0.251	-97.157	31.946	0.252
Diagnosis: SMA 1	93.001	52.390	1.775	0.136	-41.671	227.674	0.387
Ventilation: Normal	26.823	28.654	.936	0.392	-46.835	100.481	0.149
Pre-therapy growth: Underweight	-96.320	23.361	-4.123	**0.009**	-156.371	-36.268	0.773
Endurance amp Strength: Normal	-29.432	23.774	-1.238	0.271	-90.545	31.682	0.235
Position: Normal	22.124	35.281	.627	0.558	-68.568	112.817	0.073
Scoliosis: Normal	61.828	25.630	2.412	**0.061**	-4.057	127.714	0.538
Mode of feeding: Oral	15.369	37.354	0.411	0.698	-80.654	111.392	0.033
Age on Diagnosis (months)	-5.569	3.977	-1.400	0.220	-15.793	4.655	0.282
Age on first dose (months)	1.539	3.444	0.447	0.674	-7.314	10.392	0.038
Age on Gene therapy (months)	3.467	2.738	1.266	0.261	-3.571	10.505	0.243
Age (years)	-5.700	3.777	-1.509	0.192	-15.408	4.008	0.313
Intercept	-37.031	91.290	-0.406	0.702	-271.699	197.637	0.032

Regression coefficient estimates were obtained using analysis of covariance (ANCOVA) methods, with the CHOP-INTEND score (% change from pre-assessment) as the dependent variable and the potential predictor variables outlined in Table 4A. The following categories served as reference groups: gender (female), diagnosis (SMA 2), ventilation (requires respiratory support), pre-therapy growth (normal), endurance and strength (deficit), position (deficit), scoliosis (deficit), and mode of feeding (tube).Pre-therapy nutritional status was a significant predictor of motor recovery in children with SMA; underweight patients showed less improvement in CHOP-INTEND scores than those with normal growth (β = -96.32, p = 0.009). While absence of scoliosis correlated with greater motor gains (β = 61.83, p = 0.061), this was not statistically significant, likely due to sample size. Other factors—gender, SMA type, ventilation, feeding method, and age at diagnosis or therapy start—did not significantly affect outcomes.

Key points:

- Nutritional status before therapy was the only significant predictor of motor improvement.
- Absence of scoliosis had a positive but statistically insignificant association.
- Demographics and timing played minor roles.
- Optimal nutrition and musculoskeletal management may improve motor recovery in SMA.

Table 4 B Effect of various potential predictors and covariates on outcome variable percentage change from pre-assessment Hammersmith score

Predictor variables	Regression coefficient (β)	Std. Error (SE)	t-value	P-value	95% Confidence Interval for (β)		Partial Eta Squared
					Lower Bound	Upper Bound	
Gender: Male	-2.184	25.146	-0.087	0.939	-110.378	106.011	0.004
Diagnosis: SMA 1	28.083	63.226	0.444	0.700	-243.956	300.121	0.090
Ventilation: Normal	-27.517	22.117	-1.244	0.339	-122.677	67.644	0.436
Pre-therapy growth: Underweight	30.926	23.673	1.306	0.321	-70.932	132.785	0.460
Endurance amp Strength: Normal	46.555	26.894	1.731	0.226	-69.162	162.272	0.600
Position: Normal	45.216	33.170	1.363	0.306	-97.505	187.938	0.482
Scoliosis: Normal	3.005	30.666	0.098	0.931	-128.940	134.950	0.005
Mode of feeding: Oral	-61.349	40.566	-1.512	0.270	-235.893	113.194	0.533
Age on Diagnosis (months)	6.498	3.732	1.741	0.224	-9.557	22.554	0.603
Age on first dose (months)	-3.211	3.405	-0.943	0.445	-17.860	11.437	0.308
Age on Gene therapy (months)	0.706	2.852	0.247	0.828	-11.565	12.976	0.030
Age (years)	-3.722	2.690	-1.384	0.301	-15.296	7.851	0.489
Intercept	-16.619	110.494	-0.150	0.894	-492.035	458.798	0.011

Regression coefficient estimates were obtained using analysis of covariance (ANCOVA) methods, with the Hammersmith score (% change from pre-assessment) as the dependent variable and the potential predictor variables outlined in Table 4. The following categories served as reference groups: gender (female), diagnosis (SMA 2), ventilation (requires respiratory support), pre-therapy growth (normal), endurance and strength (deficit), position (deficit), scoliosis (deficit), and mode of feeding (tube).

No variable showed a statistically significant effect on Hammersmith score improvement, though participants with better baseline motor endurance and postural control had somewhat greater gains. Improvement after therapy appears multifactorial, with no single baseline factor standing out. Variables like gender, diagnosis type, ventilation, feeding mode, and age were not significantly associated with outcomes. While trends suggested that normal baseline endurance, strength, and positioning may support higher gains, these results were not statistically significant. Pre-therapy underweight status was not negatively associated with improvement, and scoliosis presence had no independent effect on changes in Hammersmith scores.

Table 5 A Association between various predictor variables with percentage change from pre-assessment CHOP-INTEND score **Statistical P-values computed using non-parametric Mann Whitney U test.*

		Percentage change from pre-assessment CHOP-INTEND score		
Predictor variables	Categories	Mean ± SD	Median (IQR)	P-value*
Gender	Male	28.12 ± 28.83	26.1 (3.5, 51.4)	0.155
	Female	26.50 ± 54.85	3.2 (0, 32.7)	

Diagnosis				
	SMA 1	34.39 ± 48.28	6.9 (0.82, 58.6)	0.552
	SMA 2	8.92 ± 10.30	4.9 (1.6, 18.2)	
Ventilation				
	Normal Ventilation	29.38 ± 45.87	4.9 (1.6, 55)	0.905
	Need Respiratory Support	16.96 ± 21.06	10.3 (0, n.a.)	
Growth-pre therapy				
	Normal	39.51 ± 47.95	26.1 (3.6, 60.4)	0.024
	underweight	2.90 ± 4.04	1.6 (0, 5.5)	
Endurance & Strength				
	Normal	26.55 ± 48.94	4.9 (1.6, 26.1)	0.682
	Deficit	28.50 ± 33.59	10.3 (0, 62.2)	
Position				
	Normal	29.91 ± 60.19	4.9 (3.2, 26.1)	0.891
	Deficit	25.66 ± 29.87	10.3 (0, 55)	
Scoliosis				
	Normal	28.38 ± 48.87	4.9 (3.2, 40.5)	0.927
	Deficit	25.63 ± 33.72	6.9 (0, 62.2)	
Mode of feeding				
	Oral	27.21 ± 48.62	4.1 (0, 47.8)	0.332
	Tube feeding	27.51 ± 30.76	18.2 (3.3, 51.1)	

Pre-therapy nutritional status was the only significant predictor of CHOP-INTEND improvement ($p = 0.024$). Children with normal nutrition showed much greater gains than underweight peers, highlighting the importance of adequate baseline nutrition for motor response after gene and rehabilitation therapies. These results confirm that malnutrition at baseline reduces therapy effectiveness, consistent with multivariable regression findings.

Table 5 B Association between various predictor variables with percentage change from pre-assessment Hammersmith score **Statistical P-values computed using non-parametric Mann Whitney U test.*

		Percentage change from pre-assessment Hammersmith score		
Predictor variables	Categories	Mean ± SD	Median (IQR)	P-value*
Gender	Male	15.82 ± 16.37	14.1 (0, 28.5)	0.907
	Female	18.41 ± 23.08	9.1 (2.6, 37.9)	
Diagnosis				
	SMA 1	14.04 ± 16.80	12.5 (0, 26.9)	0.513
	SMA 2	21.52 ± 22.97	16.0 (3.4, 38.4)	
Ventilation				
	Normal Ventilation	17.37 ± 19.79	12.5 (0.66, 28.5)	0.827
	Need Respiratory Support	15.67 ± 19.80	9.1 (0, n.a.)	
Growth-pre therapy				
	Normal	16.55 ± 21.36	8.5 (0, 28.4)	0.711
	underweight	17.99 ± 15.70	12.5 (4.5, 34.2)	
Endurance & Strength				
	Normal	19.63 ± 20.50	12.5 (2.6, 37.9)	0.291
	Deficit	9.88 ± 14.36	4.5 (0, 25.1)	
Position				
	Normal	20.10 ± 19.51	14.1 (6.5, 28.5)	0.267
	Deficit	13.52 ± 19.47	2.6 (0, 37.9)	
Scoliosis				
	Normal	14.93 ± 19.48	9.1 (0, 22.9)	0.391
	Deficit	22.81 ± 19.32	23.1 (3.9, 41.4)	
Mode of feeding				
	Oral	20.14 ± 19.11	14.1 (4.1, 32.3)	0.155
	Tube feeding	10.81 ± 19.51	4.5 (0, 36.1)	

Children with normal endurance, strength, and postural control had higher mean and median improvements than those with deficits, though differences were not statistically significant. Oral feeding participants showed better outcomes compared to tube-fed children, suggesting oral-motor ability may aid recovery. Minimal variation was observed by diagnostic category and ventilation status. Although no predictors reached significance, baseline motor function and feeding appeared positively linked to greater Hammersmith improvement, indicating these factors may support functional recovery despite limited sample size.

Table 5 C. Correlations between age, age on diagnosis, 1st dose and gene therapy with percentage change from pre-assessment CHOP-INTEND and Hammersmith scores

	Age (years)	**Age on Diagnosis (months)**		**Age on 1st dose (months)**	**Age on Gene Therapy (months)**	**CHOP-INTEND score (% Change from pre-assessment)**	**Hammersmith score (% Change from pre-assessment)**
Age (years)	Pearson Correlation	1					
Age on Diagnosis (months)	Pearson Correlation	0.335	1				
	P-value	0.160					
Age on 1st dose (months)	Pearson Correlation	0.293	0.915	1			
	P-value	0.223	0.0001				
Age on Gene Therapy (months)	Pearson Correlation	0.412	0.629	0.723	1		
	P-value	0.080	0.004	0.0001			
CHOP-INTEND score (% Change from pre-assessment)	Pearson Correlation	-0.254	-0.199	-0.211	-0.232	1	
	P-value	0.308	0.427	0.401	0.353		
Hammersmith score (% Change from pre-assessment)	Pearson Correlation	-0.331	0.398	0.307	0.153	-0.093	1
	P-value	0.228	0.141	0.267	0.586	0.751	

Functional improvements in motor (CHOP-INTEND) and mobility (Hammersmith) scores did not significantly depend on when gene therapy or supportive interventions were initiated. While earlier treatment remains clinically advantageous in general SMA management, in this study, therapeutic efficacy appeared consistent across age ranges, likely influenced more by baseline nutritional and functional status than by age or treatment timing variables.

4. Discussion

This retrospective study shows that combining gene therapy with intensive multidisciplinary rehabilitation significantly improves motor function in children with SMA Types 1 and 2. Most participants saw notable gains, regardless of baseline differences, highlighting this approach's broad relevance. Improvements were closely tied to preserved respiratory function and good nutritional status before therapy; those needing ventilatory support did not improve, while well-nourished patients responded best. Importantly, pre-therapy malnutrition greatly reduced recovery potential, though nutritional status often improved after treatment.

Rehabilitation for SMA is now restorative, especially with disease-modifying therapies. Structured programs—including physiotherapy, occupational, speech, respiratory support, and nutrition—are effective when paired with gene therapy. Intensive, frequent rehabilitation across several disciplines correlates with better outcomes, suggesting proactive care should be standard post-gene therapy.

Key predictors of success include stable respiratory function and adequate nutrition prior to treatment. Early intervention, thorough nutrition assessment, and respiratory management are recommended. Treatment timing within symptomatic patients was less influential than respiratory and nutritional status, indicating aggressive interventions remain beneficial beyond presymptomatic cases. Clinical practice should combine gene therapy with comprehensive

rehabilitation and pre-treatment optimization. Individualized plans, ongoing outcome tracking, and coordinated care are essential for maximizing patient improvements.

Abbreviations and Acronyms

List abbreviations, acronyms and terms of reference used in the protocol; provide definitions for each as needed

- SMA : Spinal muscular atrophy
- SMN : survival motor neuron
- ADL : Activities of daily living
- FTT: Failure To Thrive
- BMI: Body Mass Index
- FDA : Food and Drug Administration
- EMA : European Medicines Agency
- WHO : World Health Organization
- CDC : Centers for Disease Control and Prevention
- ROM : Range of Motion
- CHOP INTEND: Children Hospital of Philadelphia Infant Test of Neuromuscular Disorders
- HINE : Hammersmith Infant Neurological Examination
- QRI : Qatar rehabilitation Institute
- SD: Standard deviation; CI: Confidence interval

5. Conclusion

This retrospective study shows strong evidence that combining gene therapy with intensive, multidisciplinary rehabilitation can greatly improve motor function in children with SMA Types 1 and 2. Improvements in CHOP-INTEND and Hammersmith scores were observed, with 79% of patients showing functional gains—demonstrating how effective this integrated treatment is in real clinical settings.

Importantly, having stable respiratory function and good nutrition before starting therapy were found to be critical factors that can influence treatment success. Patients who needed ventilatory support did not improve, whereas those with normal breathing had excellent results. Poor nutrition before therapy was independently linked to much smaller improvements in motor function, explaining most of the differences in outcomes. Therefore, making sure children have optimal nutrition and managed respiratory health before treatment should be a priority to get the best results from gene therapy.

The study's intensive rehabilitation model—which included physiotherapy, occupational therapy, speech therapy, respiratory care, and nutritional support (3–5 sessions each week)—proved successful and is recommended as standard care for SMA patients getting disease-modifying treatments. Healthcare systems must make sure that gene therapy is supported by comprehensive rehabilitation services to achieve the best possible outcomes.

Although the study's small size and retrospective nature are limitations, its consistent findings across different analyses provide convincing support for this approach. Larger, controlled studies are needed in the future to fine-tune rehabilitation protocols, discover more factors that affect response, and track long-term results.

For pediatric SMA patients and their families, these results offer hope: with timely access to disease-modifying treatments, proper nutrition, maintained respiratory function, and intensive rehab, significant improvements are possible, regardless of starting condition or age. Ongoing research and new clinical methods will continue to improve prospects for this vulnerable group.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was waived due to the retrospective nature of the study, as approved by the Medical Research Center.

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