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# Multisystemic Evaluation in Pediatric Spinal Muscular Atrophy: Linking Biochemical Markers to Functional Outcomes and Family Quality of Life

## Pediatrik Spinal Müsküler Atrofide Multisistemik Değerlendirme: Biyokimyasal Belirteçlerin Fonksiyonel Sonuçlar ve Aile Yaşam Kalitesi ile İlişkisi

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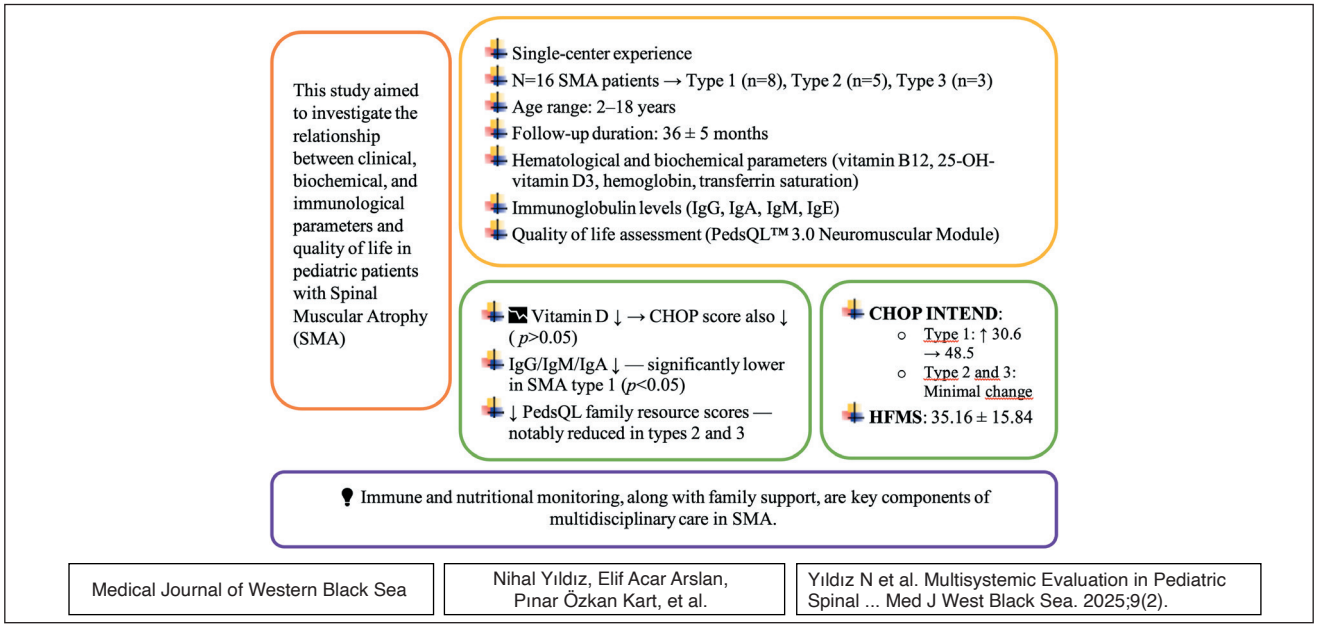
**GRAPHICAL ABSTRACT**

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## ABSTRACT

**Aim:** Spinal Muscular Atrophy (SMA) is a rare neuromuscular disorder requiring a multidisciplinary approach. This study aimed to investigate the clinical, biochemical, and immunological parameters in pediatric SMA patients and to explore their potential associations with quality of life.

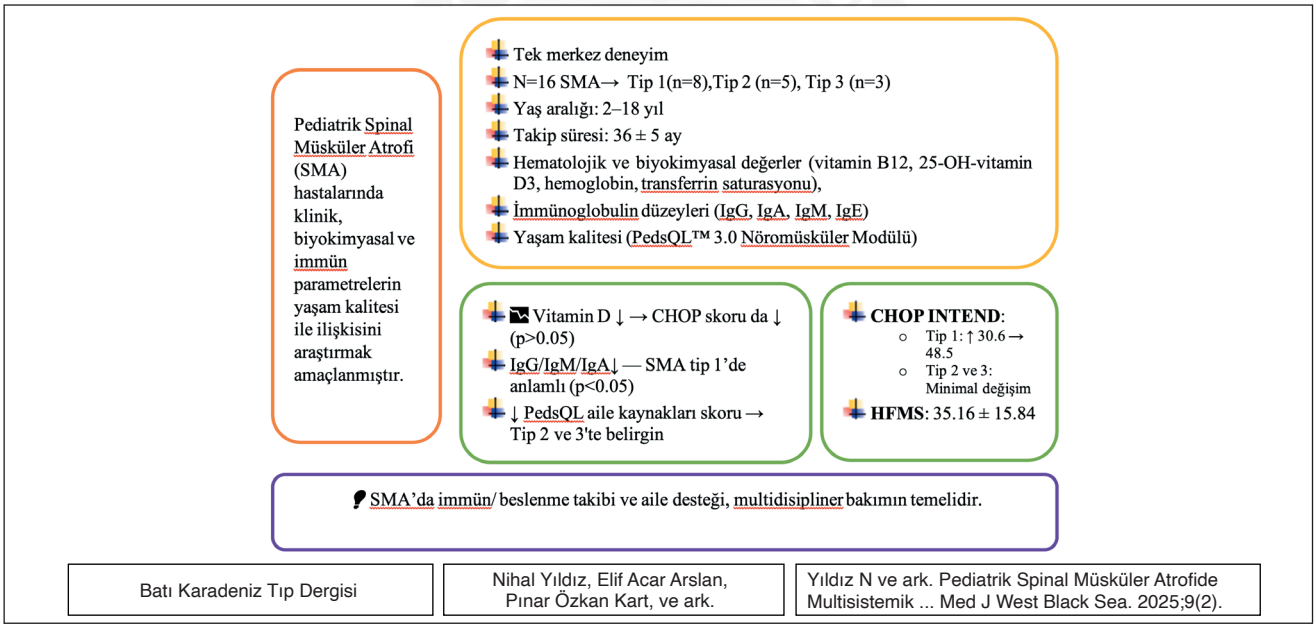
**Material and Methods:** In this study, 16 genetically confirmed SMA patients aged 2–18 years were evaluated. Data on hematologic and biochemical profiles, including vitamin B12, 25-OH-vitamin D3, and immunoglobulin levels, were recorded. The PedsQL™ 3.0 Neuromuscular Module was administered to assess quality of life.

**Results:** The cohort included 8 patients with SMA type 1, 5 with type 2, and 3 with type 3. Seven (43.75%) were females, with a mean age of 93±60 months. The mean follow-up period was 36±5 months. Serum vitamin B12 values were 271±66ng/L, and 25-OH-D3 vitamin values were 21.14±12.9*μ*g/L. Immunoglobulin (Ig) G levels of 5 (31.25%) were below the normal range for their ages. When SMAtype1, SMA type2, and 3 groups were compared, there was no difference in vitamin B12, vitamin D, and IgE levels. Hemoglobin and transferrin saturation were significantly lower in SMA type 1 patients($p<0.05$). According to the quality of life assessment of SMA type 2 and 3 patients reported greater financial concerns. All children who completed the questionnaire had similarly low scores. While a decrease in vitamin D level was associated with lower CHOP scores, the relationship was not statistically significant.

**Conclusion:** Even in small cohorts, periodic evaluation of immune and nutritional parameters may reveal clinically relevant findings in SMA. These factors, along with tailored support for families, should be considered in long-term multidisciplinary management.


**Keywords:** Immunoglobulin, multidisciplinary care, spinal muscular atrophy, vitamin D level, quality of life

**GRAFİKSEL ÖZET**





## ÖZ

**Amaç:** Spinal Müsküler Atrofi (SMA), multidisipliner yaklaşım gerektiren nadir bir nöromüsküler hastalıktır. Bu çalışmada, pediatrik SMA hastalarında klinik, biyokimyasal ve immünolojik parametrelerin değerlendirilmesi ve bu parametrelerin yaşam kalitesi ile olası ilişkilerinin araştırılması amaçlanmıştır.

**Gereç ve Yöntemler:** Bu çalışmaya, genetik olarak doğrulanmış ve yaşları 2–18 arasında değişen 16 SMA hastası dahil edilmiştir. Hastaların hemogram ve biyokimyasal profilleri, özellikle vitamin B12, 25-OH-vitamin D3 ve immünoglobulin düzeyleri kaydedilmiştir. Yaşam kalitesini değerlendirmek amacıyla PedsQL™ 3.0 Nöromüsküler Modülü uygulanmıştır.

**Bulgular:** Çalışma grubunu 8 SMA tip 1, 5 SMA tip 2 ve 3 SMA tip 3 hastası oluşturmuştur. Katılımcıların 7'si (%43,75) kız, ortalama yaşları 93±60 aydır. Ortalama takip süresi 36±5 ay olarak belirlenmiştir. Serum vitamin B12 düzeyi ortalama 271±66 ng/L, 25-OH-D3 düzeyi ise 21,14±12,9 *μ*g/L olarak saptanmıştır. Beş hastada (%31,25) yaşlarına göre düşük immünoglobulin G (IgG) düzeyleri tespit edilmiştir. SMA tip 1, 2 ve 3 grupları karşılaştırıldığında, vitamin B12 ve D düzeyleri açısından anlamlı fark bulunmamıştır. Ancak hemoglobin düzeyi ve transferrin saturasyonu SMA tip 1 hastalarında anlamlı olarak daha düşüktü ($p<0,05$). Yaşam kalitesi değerlendirme ölçeğinde, özellikle SMA tip 2 ve 3 hasta ailelerinde finansal kaygıların ön planda olduğu, tüm çocukların ise benzer skorlar aldığı görülmüştür. Vitamin D düzeyleri

ile anket sonuçları karşılaştırıldığında, düşük vitamin D düzeylerinin CHOP skorundaki düşüşle ilişkili olduğu gözlenmiş; ancak bu ilişki istatistiksel olarak anlamlı bulunmamıştır.

**Sonuç:** Küçük örneklem gruplarında dahi, immün ve beslenme ile ilişkili parametrelerin periyodik olarak değerlendirilmesi, SMA hastalarında klinik açıdan anlamlı bulguların ortaya konmasına katkı sağlayabilir. Bu faktörler ve ailelere yönelik bireyselleştirilmiş destek mekanizmaları, uzun vadeli multidisipliner izlem planlarında dikkate alınmalıdır.

**Anahtar Sözcükler:** İmmünoglobulin, multidisipliner bakım, Spinal müsküler atrofi, vitamin D düzeyi, yaşam kalitesi

## INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by progressive muscle atrophy and motor neuron loss, with an estimated incidence of 1 in 10,000 live births (1,2). Mutations or deletions in the SMN1 gene on chromosome 5q13 lead to the clinical manifestations of SMA (3).

Patients are classified into types 1, 2, or 3 depending on symptom onset and severity, with type 1 being the most severe form (4).

Life expectancy has significantly improved with the advent of disease-modifying treatments, with nusinersen being the first approved therapy in 2016 (5). The safe treatment profile of nusinersen has been highlighted in previous studies (6,7).

Due to its multisystemic nature, SMA involves not only motor impairment but also respiratory, nutritional, and orthopedic complications (8). Hence, regular follow-up by a multidisciplinary team is essential.

Quality of life assessments, such as the PedsQL 3.0 Neuromuscular Module, are valuable for identifying patient and caregiver challenges and tailoring care accordingly (9).

Although several studies have addressed the quality of life in SMA, few have incorporated laboratory markers such as immunoglobulin and micronutrient levels. This study aims to bridge that gap by correlating clinical and biochemical parameters with quality of life outcomes in a pediatric SMA cohort from a single center. Given the rarity and heterogeneity of SMA, even small sample studies contribute valuable insights to individualized care planning and future therapeutic research.

## MATERIALS and METHODS

Following ethics committee approval, 16 genetically confirmed SMA patients aged 2–18 years who presented to a single tertiary pediatric neurology clinic between 2015 and 2021 were included in this descriptive case series. Clinical data, including demographics, motor milestones, and functional motor scores (CHOP INTEND, HFMS), were collected from medical records.

Biochemical parameters included complete blood count, iron studies, vitamin B12, 25-OH vitamin D3, thyroid function ~~tests~~, and immunoglobulin (IgG, IgA, IgM, IgE) levels. These were assessed from outpatient visits.

The PedsQL 3.0 Neuromuscular Module questionnaire, which is appropriate for the age group of the child, was administered to the families who came for a check-up. The 25-item PedsQL™ 3.0 Neuromuscular Module includes three scales: 1) About My/My Child's Neuromuscular Disease (17 items regarding the disease process and associated symptomatology), 2) Communication (three items regarding the patient's ability to communicate with healthcare providers and others about the disease), and 3) About Our Family Resources (five items regarding family financial and social support systems).

The PedsQL™ Neuromuscular Module Scales consist of parallel child self-report and parent proxy report formats for children ages 5 to 18 years and a parent proxy report format for children ages 2 to 4 years. The format, instructions, Likert response scale, and scoring method for the PedsQL™ 3.0 Neuromuscular Module are the same as the PedsQL™ 4.0 General Core Scales, including child self-report formats for ages 5–7, 8–12, and 13–18, and parent proxy report formats for ages 2–4, 5–7, 8–12, and 13–18. The younger child form (ages 5–7) does not include the Communication and About Our Family Resources Scales because current field testing has found that Cronbach's alpha for these two scales is in the unacceptable range for children ages 5–7. Items are linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0) such that higher scores indicate better HRQOL. Scale scores are calculated by dividing the sum of the items by the number of items answered.

The PedsQL™ 3.0 Neuromuscular Module was developed using the authors' research and clinical experience with neuromuscular disorders such as SMA and Duchenne Muscular Dystrophy (DMD) and other chronic conditions, and using the methodology documented by Varni et al. (10-13).

Data were analyzed using SPSS v22.0. The Kolmogorov-Smirnov test was used for normality assessment. Given the small sample size, only descriptive statistics were used. Continuous variables were expressed as mean ± standard deviation (SD) and range, while categorical variables were presented as frequencies and percentages.

## RESULTS

Among the 16 patients included (8 with SMA type 1, 5 with type 2, 3 with type 3), the mean age was 93 ± 60 months, and 7 (43.75%) were female. The mean follow-up period was 36 ± 5 months.

In the SMA type 1 group, the mean age at diagnosis was 28 months (range: 2-57), and age at presentation was 1-45 months. The mean initial CHOP score was 30.6 ± 18, while the ~~mean~~ final CHOP score was 48.5 ± 18.65. For SMA type 2, the mean age at diagnosis was 45 ± 1 months, and age at presentation was 6-120 months. The initial CHOP score was 19.4±16. And the final CHOP score was 28.6. In SMA type 3, the mean age at diagnosis was 45 months, and the CHOP score changed from 43.6 ± 16.5 to 42.6 ± 13. The mean HFMS score was 35.16 ± 15.84, and the mean CHOP INTEND score was 31.0 ± 17.62.

Mean serum vitamin B12 was 271±66ng/L, 25-OH-D3 vitamin was 21.14±12.9μg/L, hemoglobin was 12.1±1 g/dL, and transferrin saturation was 16±2 μg/dL. Immunoglobulin (Ig) G levels of 5 (31.25%) were below the normal values for their ages: Ig G (immunoglobulin G) value was 468.5±334.13 mg/dL, Ig M: 69.34±45.19 mg/dL, Ig A value was 54.2±59 mg/dL. IgG levels of four cases were below the normal value for their ages. While no significant differences were observed in vitamin B12, vitamin D, or IgE levels across SMA types, hemoglobin, transferrin saturation, IgG, IgM, and IgA levels were significantly lower in type 1 SMA patients ($p<0.05$). Laboratory findings of the cases according to SMA types are given in detail in Table 1. Four patients had other chronic diagnoses: major depression (n=1), pulmonary infection (n=1), epilepsy (n=1), and immunodeficiency (n=1).

**Table 1:** The laboratory findings according to SMA types

| | SMA Type 1 | SMA Type 2 | SMA Type 3 |
|---|---|---|---|
| The mean first hemogram levels | 11.7± 1 (9.8-13.5) | 12.2 ± 1.17 (10.6-13.90) | 12.6 ± 0.5 (12.10-13.20) |
| The Mean last hemogram levels | 12.03± 1.2 (10-13.80) | 12.1± 2.1 (8.4-13.7) | 13.3 ± 0.2 (12.9-13.9) |
| The Mean Iron levels | 46.7 ± 14.9 (34-72) | 52.4 ± 29.9 (10-84) | 79 ± 19.9 (56-91) |
| The Mean Iron binding capacity | 283 ± 33.4 (236-333) | 315 ± 57 (232-376) | 336 ± 57.3 (271-377) |
| The Mean ferritin levels | 28.7 ± 8.6 (17.6-43.7) | 17 ± 9.7 (4.3-30) | 23.3 ± 9 (14-32) |
| The Mean vitamin D levels | 31.9 ± 13.8 (6.99-51.45) | 18.94 ± 16.5 (4.58-43.09) | 16.49 ± 6.95 (8.54-21.4) |
| The Mean vitamin B12 levels | 270 ± 132 (75-479) | 378 ± 232 (161-718) | 291 ± 84.8 (211-380) |

In addition, when the PedsQL 3.0 Neuromuscular Module scores were examined, it was found that respiratory and nutritional support were among the most burdensome issues reported by families. Financial strain was more frequently reported in families and the patients of SMA types 2 and 3.

A significant decrease was observed in CHOP INTEND scores as vitamin D levels decreased, but this relationship was not statistically significant ($p>0.05$). In the family quality of life assessment scale, it was observed that families in the SMA 2 and 3 groups had a significant decrease in the family resources section, while all children were observed to have low scores in the same section.

Patients were examined for detailed intrathecal side effects (hydrocephalus, renal cyst, scoliosis, failure to receive IT, factor level problem). Although there were no patients with drug side effects, only 1 case had a severe headache after IT treatment; cranial imaging was normal.

## DISCUSSION

This study evaluated the associations between biochemical parameters, particularly vitamin D, vitamin B12, and immunoglobulin levels, and clinical severity and quality of life in children with SMA. Our findings suggest that certain laboratory abnormalities may reflect underlying vulnerabilities that impact both motor function and overall well-being.

Recent findings from the 264th ENMC International Workshop underscore the multisystemic pathology of SMA, involving not only motor neuron degeneration but also a range of peripheral organ systems, including skeletal muscle, immune system, cardiac tissue, and metabolic regulation. This substantiates the rationale for integrating biochemical and immunological markers into comprehensive clinical assessments in pediatric SMA (14).

Vitamin D deficiency was prevalent in our cohort, consistent with previous studies indicating an increased risk of osteoporosis and fractures in SMA patients (10,15). Although a positive trend was observed between vitamin D levels and CHOP INTEND scores, this relationship did not reach statistical significance ($p > 0.05$). This finding is consistent with the study by Aton et al., which reported an association between vitamin D deficiency and reduced bone mineral density and motor performance in SMA patients (10). In our study, the relationship between vitamin D levels and motor function did not reach statistical significance, possibly due to the small sample size, retrospective design, and inter-patient variability in vitamin D supplementation. Nonetheless, this finding supports the need for routine screening and supplementation to maintain musculoskeletal health in SMA.

Immunologic evaluation revealed that IgG, IgA, and IgM levels were significantly lower in SMA type 1 patients ($p < 0.05$), suggesting greater immunological vulnerability. This is in line with existing literature documenting recurrent respiratory infections in SMA, primarily due to respiratory muscle weakness and dysphagia (16). These findings highlight the importance of routine immune monitoring and infection prevention strategies in clinical management. Furthermore, they may justify regular assessment of immunoglobulin levels in SMA type 1 patients and raise the consideration of prophylactic interventions, such as booster vaccinations or antibiotic prophylaxis, to mitigate infection risk in this particularly susceptible subgroup (14).

The quality of life results, as assessed by the PedsQL 3.0 Neuromuscular Module, indicated that respiratory and nutritional dependencies were the most significant contributors to caregiver burden. Families of SMA type 2 and 3 patients reported particularly high financial concerns, reflected by lower scores in the family resources subscale. This underscores the importance of integrating socioeconomic support into SMA care plans.

This study underscores the importance of monitoring nutritional and immunologic parameters in SMA, as these may influence disease progression and patient well-being. Regular assessment of vitamin D levels and individualized nutritional strategies are critical for maintaining bone health and supporting neuromuscular function. Similarly, identifying immunoglobulin deficiencies may guide infection prevention and immunological support in vulnerable subgroups, especially those with SMA type 1. Since vitamin D and immunoglobulin deficiencies are low-cost to detect and potentially correctable, their inclusion in routine follow-up may yield significant clinical benefits with minimal resource burden.

From a psychosocial perspective, the evaluation of caregiver-reported outcomes revealed that respiratory and nutritional dependencies significantly contribute to caregiver burden. Financial strain was particularly notable among families of SMA type 2 and 3 patients, highlighting the necessity of incorporating socioeconomic support into multidisciplinary care plans.

Multidisciplinary models that integrate medical, nutritional, immunological, and psychosocial components are essential for optimizing outcomes in SMA. In addition to improving functional status and reducing caregiver burden (13), consistent multidisciplinary follow-up plays a pivotal role in delaying disease progression and preventing complications.

However, due to the heterogeneous timing of nusinersen initiation among patients, a consistent pre- and post-treatment comparison of laboratory or quality of life parameters was not feasible. Future prospective studies may address this temporal variation more systematically. Moreover, larger multicenter cohorts are needed to validate these preliminary findings and enhance their generalizability to broader SMA populations. Holistic care that includes regular quality of life assessments for both patients and families should be regarded as a central element of long-term SMA management.

### Conclusion

Even in small cohorts, a comprehensive evaluation of immune and nutritional parameters can provide valuable insights into the multisystemic burden of SMA. Routine quality of life assessments and family-centered interventions remain essential components of a holistic care strategy aimed at improving both clinical outcomes and overall well-being.

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**Author Contributions**

The authors confirm contribution to the paper as follows: Study conception and design: **Nihal Yıldız, Elif Acar Arslan,** data collection: **Nihal Yıldız, Pınar Özkan Kart, Sevim Şahin, Tülay Kamaşak,** analysis and interpretation of results: **Nihal Yıldız, Elif Acar Arslan;** draft manuscript preparation: **Nihal Yıldız, Ali Cansu.** All authors reviewed the results and approved the final version of the manuscript.

**Conflicts of Interest**

All authors declare that they have no conflict of interest

**Financial Support**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Ethical Approval**

Ethics Committee number: 2022/226-619.

**Review Process**

Extremely and externally peer-reviewed.

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