Original Article
Yonsei Med J 2024 Oct;65(10):572-577
https://doi.org/10.3349/ymj.2023.0557
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

# Diagnostic Journey of Korean Patients with Spinal Muscular Atrophy

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**Purpose:** Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease characterized by the loss of motor neurons in the spinal cord and brainstem, leading to muscle atrophy and weakness. To understand the diagnostic process of Korean patients with SMA, we analyzed their clinical characteristics and challenges.

**Materials and Methods:** We conducted a retrospective study of 38 patients with SMA (9 type II and 29 type III) between January 2000 and September 2023. Clinical, laboratory, and genetic data were reviewed.

**Results:** The median ages at symptom onset and diagnosis were 3.0 years [interquartile range (IQR): 1.0–7.3 years] and 25.0 years (IQR: 10.5–37.3 years), respectively. The median diagnostic delay was 19.6 years (IQR: 6.4–31.0 years). A significantly longer delay was observed in SMA type III patients (median: 21.0 years, IQR: 11.0–31.0 years) compared to SMA type II patients (median: 3.0 years, IQR: 0.9–21.0 years) ($p$=0.021). No significant difference was observed in the number of clinic visits before diagnosis between patients with SMA type II (median: 2.0, IQR: 1.0–4.5) and those with type III (median: 2.0, IQR: 2.0–6.0, $p$=0.282). The number of clinic visits before diagnosis showed no significant association with the age at symptom onset and diagnosis ($p$=0.998 and 0.291, respectively).

**Conclusion:** Our investigation is the first examination of the diagnostic journey of Korean patients with SMA. As treatments for SMA progress, the significance of an accurate diagnosis has increased, highlighting the importance of reviewing the diagnostic advancements made thus far.

**Key Words:** Spinal muscular atrophy, SMN1, diagnostic delay, diagnostic odyssey

## INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease characterized by progressive degeneration and loss of motor neurons in the spinal cord and brainstem, leading to muscle atrophy and weakness. It is primarily caused by pathogenic variants of survivor motor neuron 1 (*SMN1*), leading to reduced levels of the functional, full-length survivor motor neuron protein.[1-3] The severity is partially influenced by the copy number of the *SMN2* gene, a homologue of *SMN1*. *SMN2* produces about 10% of the functional protein compared to *SMN1*, contributing to the variability in SMA severity.[4] The common clinical presentation of SMA includes weakness and atrophy of proximal muscles, areflexia, scoliosis, and respiratory impairment. However, symptom onset and disease severity differ among subtypes: type I (non-sitter), type II (independent sitting when placed), type III (independent ambulation), and type IV (adult onset).[5,6]

Recent advancements in SMA therapies, including nusinersen, risdiplam, and the onasemnogene abeparvovec-xioi, have transformed the landscape of SMA management.[7-10] Therefore,

**Received:** January 5, 2024 **Revised:** April 3, 2024
**Accepted:** April 4, 2024 **Published online:** July 9, 2024
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•The authors have no potential conflicts of interest to disclose.

early and accurate diagnosis of SMA has become increasingly crucial.[7,8] The gold standard for diagnosis is genetic testing of *SMN1* in patients with suspected SMA.[11] Needle electromyography (EMG) and pathological studies of biopsied muscles also support the diagnosis of SMA. However, delays in diagnosis are still common due to its clinical similarities with other neuromuscular disorders.[12] Several challenges remain for the early and accurate diagnosis of SMA, including the need for specialized expertise, facilities for genetic testing, low disease awareness, and variability in disease symptoms. These factors contribute to misdiagnoses and delayed diagnoses of SMA.[12] Previous studies on the difficulties of the diagnostic process in the real world have mainly focused on pediatric SMA patients.[9,12,13] To our knowledge, no study has analyzed the difficulties of the diagnostic process in adults with SMA. However, adults with SMA are more frequently misdiagnosed with muscular dystrophy than pediatric patients due to similarities in the diseases' clinical features.[14]

To better understand the diagnostic process in Korean patients with SMA, we analyzed their clinical characteristics and challenges.

## MATERIALS AND METHODS

### Study participants

We reviewed the medical records of patients with neuromuscular disorders who were referred to the Department of Neurology of Gangnam Severance Hospital between January 2000 and September 2023. Our study included patients who visited the neurology department at our hospital and received a diagnosis confirmed through genetic testing. Among these records, 39 patients with SMA were identified: 9 with SMA type II, 29 with SMA type III, and one with SMA type IV. However, individuals with SMA type IV who did not exhibit muscle weakness and were diagnosed based on their family history were excluded from the study. This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Korea (approval number: 3-2023-0364). The requirement for written informed consent was waived by the board owing to stringent anonymization protocols, ensuring complete confidentiality of personal information.

### Phenotype assessment

Clinical and laboratory data were retrospectively obtained by reviewing medical records. The clinical information included sex, age at symptom onset, age at diagnosis, diagnostic delay, initial symptoms, previously misdiagnosed medical conditions, number of clinic visits before diagnosis, assessment of muscle impairment, presence of scoliosis, respiratory difficulty, and ventilator use. Laboratory analysis was performed to assess serum creatine kinase (CK) levels. SMA was categorized based on the age at symptom onset: type I, presenting between birth and 6 months; type II, onset between 7 and 18 months; type III, onset between 18 months and 18 years of age; and type IV, onset occurring after 18 years of age.[15] Age at diagnosis was defined as the age at which SMA was confirmed through genetic testing. Diagnostic delay was defined as the duration between the onset of symptoms and the age at diagnosis. The number of clinic visits before diagnosis was defined as the total number of visits to all healthcare facilities, including neurology, orthopedics, pediatrics, and other departments, before an SMA diagnosis is confirmed through genetic testing. To collect data on the actual number of clinic visits before diagnosis, we reviewed electronic medical records and conducted surveys with patients and their caregivers through telephone calls and direct interviews.

### Statistical analysis

The chi-square test was used to compare discrete variables, and Fisher's exact test was used for variables with a cell number of less than five. For comparisons between the SMA type II and type III groups in terms of age at symptom onset, age at diagnosis, diagnostic delay, number of clinic visits before diagnosis, and serum CK level, the Mann-Whitney U test was employed. The Kruskal–Wallis test with Dunn's post hoc test was used to compare the age at symptom onset, age at diagnosis, diagnostic delay, and number of clinic visits before diagnosis across distinct time periods (1996–2004, 2005–2013, and 2014–2022). Spearman's correlation analysis was conducted to evaluate the relationships between age at symptom onset, age at diagnosis, and the number of clinic visits before diagnosis. All *p*-values were two-tailed, and values below 0.05 were considered statistically significant. Statistical analysis was performed using R software (version 4.3.2), obtained from www.r-project.org.

## RESULTS

### Demographic and genetic analysis

The study comprised 38 patients with SMA (18 males and 20 females), with 9 classified as type II and 29 as type III. Median ages at symptom onset and diagnosis were 3.0 years [interquartile range (IQR): 1.0–7.3 years] and 25.0 years (IQR: 10.5–37.3 years), respectively (Table 1). All 38 patients exhibited deletions in exons 7 and 8 of *SMN1*. Of the 25 patients analyzed for *SMN2* copy numbers (6 in type II and 19 in type III), all type II patients had three copies (Fig. 1A), while in type III patients, 8 (42%) had three copies and 11 (58%) had four copies (Fig. 1B).

### Diagnostic delay

Median diagnostic delay was 19.6 years (IQR: 6.4–31.0 years). The delay was significantly longer in SMA type III patients (median: 21.0 years, IQR: 11.0–31.0 years) than in SMA type II patients (median: 3.0 years, IQR: 0.9–21.0 years) ($p$=0.021). No significant difference was observed in the number of clinic vis-

**Table 1.** Clinical Characteristics of SMA Patients

| | Total (n=38) | SMA type II (n=9) | SMA type III (n=29) | *p* value |
|---|---|---|---|---|
| Sex male | 18 (47) | 6 (67) | 12 (41) | 0.260 |
| Age at symptom onset, yr | 3.0 (1.0–7.3) | 1.0 (0.8–1.0) | 5.0 (2.5–8.0) | <0.001 |
| Diagnostic delay, yr | 19.6 (6.4–31.0) | 3.0 (0.9–21.0) | 21.0 (11.0–31.0) | 0.021 |
| Age at diagnosis, yr | 25.0 (10.5–37.3) | 4.0 (1.8–22.0) | 32.0 (19.0–38.0) | 0.003 |
| Number of clinic visits before diagnosis | 2.0 (2.0–6.0) | 2.0 (1.0–4.5) | 2.0 (2.0–6.0) | 0.282 |
| Initial clinical symptoms | | | | |
| Unsteady ambulation | 22 (58) | 0 (0) | 22 (76) | <0.001 |
| Running difficulty | 7 (18) | 0 (0) | 7 (24) | 0.164 |
| Difficulty in rising from the floor | 2 (5) | 0 (0) | 2 (7) | >0.999 |
| Delayed development of sitting posture | 10 (26) | 9 (100) | 1 (3) | <0.001 |
| Delayed development of standing posture | 2 (5) | 0 (0) | 2 (7) | >0.999 |
| Initially misdiagnosed medical conditions | | | | |
| Total misdiagnosed medical conditions | 24 (63) | 5 (56) | 19 (66) | 0.699 |
| Muscular dystrophy | 18 (48) | 1 (11) | 17 (59) | 0.021 |
| Developmental delay | 6 (16) | 5 (56) | 1 (3) | 0.001 |
| Cerebral palsy | 3 (8) | 0 (0) | 3 (10) | >0.999 |
| Kennedy disease | 1 (3) | 0 (0) | 1 (3) | >0.999 |
| Clinical features at diagnosis | | | | |
| Proximal muscle weakness | 38 (100) | 9 (100) | 29 (100) | >0.999 |
| Scoliosis | 30 (79) | 9 (100) | 21 (72) | 0.159 |
| Respiratory difficulty | 24 (63) | 8 (89) | 16 (55) | 0.115 |
| Ventilator use | 9 (22) | 5 (56) | 4 (14) | 0.020 |
| Serum CK level | 85.0 (32.5–182.3) | 34.0 (27.5–129.5) | 113.0 (41.5–350.0) | 0.131 |

SMA, spinal muscular atrophy; CK, creatine kinase.
Data are presented as n (%) or median (interquartile range).

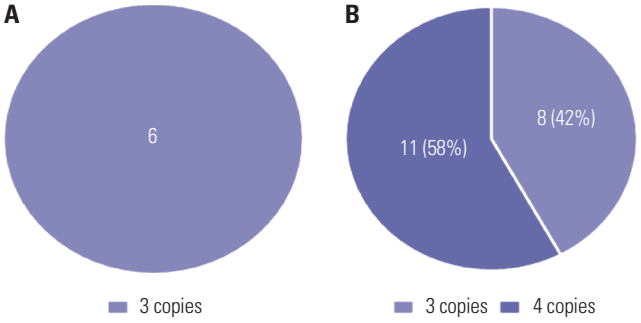


**Fig. 1.** Distribution of *SMN2* copy numbers in 25 Korean patients with SMA. (A) SMA type II (n=6). (B) SMA type III (n=19). SMA, spinal muscular atrophy.

its before diagnosis between type II (median: 2.0, IQR: 1.0–4.5) and type III (median: 2.0, IQR: 2.0–6.0, $p$=0.282). The number of clinic visits before diagnosis was not significantly associated with the age at symptom onset or diagnosis ($p$=0.998 and 0.291, respectively) (Fig. 2).

## Clinical presentation and assessment

Table 1 shows the clinical presentation at symptom onset and diagnosis according to subtype. The most common initial symptoms were delayed development of sitting posture in type II and unsteady ambulation in type III. Initial misdiagnosis occurred in two-thirds of the cases, with no significant difference between type II (n=5, 56%) and type III (n=19, 66%, $p$=0.699). Different misdiagnosed conditions were observed in type II (developmental delay) and type III (muscular dystrophy). At diagnosis, all patients exhibited proximal muscle weakness. Mechanical ventilator use was significantly higher in type II (n=5, 56%) than in type III (n=4, 14%; $p$=0.020). No significant difference in serum CK levels was found between type II (median: 34.0, IQR: 27.5–129.5) and type III (median: 113.0, IQR: 41.5–350.0, $p$=0.131).

Table 2 shows the assessments performed before a confirmed diagnosis of SMA. The most common assessment was needle EMG in 35 patients (92%), followed by muscle biopsy in 22 patients (58%), and genetic testing for muscular dystrophy in 20 patients (53%). Genetic testing for muscular dystrophy was significantly more prevalent in type III (n=18, 62%) than in type II (n=1, 11%, $p$=0.019).

## Changes over time

Table 3 shows that the age at symptom onset ($p$=0.008), age at diagnosis ($p$<0.001), and diagnostic delay ($p$=0.001) were significantly different across distinct periods: 1996–2004, 2005–2013, and 2014–2022. The age at symptom onset significantly increased during the 2005–2013 period (Dunn's post hoc test, $p$=0.033) and the 2014–2022 period (Dunn's post hoc test, $p$=


https://doi.org/10.3349/ymj.2023.0557

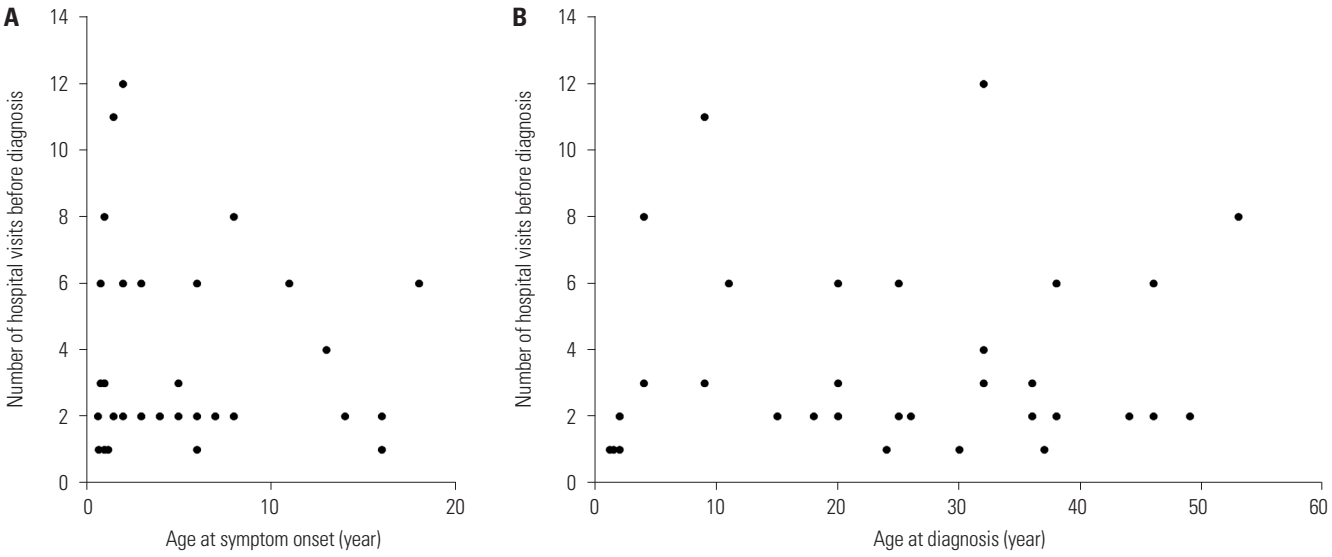


**Fig. 2.** Correlation of the number of clinic visits before diagnosis with the age at symptom onset and diagnosis. (A) The scatter plot before diagnosis was not significantly associated with the age at symptom onset (A) or diagnosis (B) ($p$=0.998 and 0.291, respectively).

**Table 2.** Assessments Performed before a Confirmed Diagnosis of SMA

| | Total (n=38) | SMA type II (n=9) | SMA type III (n= 29) | *p* value |
|---|---|---|---|---|
| Needle electromyography | 35 (92) | 7 (78) | 28 (97) | 0.134 |
| Muscle biopsy | 22 (58) | 7 (78) | 15 (52) | 0.254 |
| Brain MRI | 3 (8) | 1 (11) | 2 (7) | >0.999 |
| Genetic testing for myopathy | 20 (53) | 1 (11) | 18 (62) | 0.019 |

SMA, spinal muscular atrophy; MRI, magnetic resonance imaging.
Data are presented as n (%).

**Table 3.** Differences in Age at Symptom Onset and Diagnosis According to Time Intervals

| | 1996–2004 (n=9) | 2005–2013 (n=17) | 2014–2022 (n=12) | *p* value |
|---|---|---|---|---|
| Age at symptom onset, yrs*† | 1.0 (1.0–2.3) | 3.0 (1.4–7.5) | 6.5 (2.8–11.8) | 0.008 |
| Age at diagnosis, yrs*†‡ | 4.0 (1.8–14.5) | 20.0 (15.0–32.0) | 37.5 (33.0–45.5) | <0.001 |
| Diagnostic delay, yrs†‡ | 3.0 (0.9–12.5) | 17.0 (6.5–27.0) | 29.5 (21.5–40.8) | 0.001 |
| Number of clinic visits before diagnosis | 3.0 (1.5–5.5) | 2.0 (2.0–4.5) | 2.0 (2.0–6.0) | 0.932 |

Data are presented as median (interquartile range).
*Significant differences between the periods of 1996–2004 and 2005–2013 (Dunn's post hoc test, $p$<0.05); †Significant differences between the periods of 1996–2004 and 2014–2022 (Dunn's post hoc test, $p$<0.05); ‡Significant differences between the periods of 2005–2013 and 2014–2022 (Dunn's post hoc test, $p$<0.05).

0.002) compared to the 1996–2004 period. Dunn's post hoc test indicates a notably higher age at diagnosis throughout different time periods (1996–2004, 2005–2013, and 2014–2022). Diagnostic delay significantly extended during the 2014–2022 period compared to the 1996–2004 period (Dunn's post hoc test, $p$< 0.001) and the 2005–2013 period (Dunn's post hoc test, $p$=0.011). However, the number of clinic visits before diagnosis was not significantly different across distinct periods ($p$=0.932).

## DISCUSSION

To our knowledge, our study is the first to investigate the diagnostic journey of patients with SMA in Korea. Clinically, proximal muscle weakness was observed in all patients, with scoliosis in 80% and respiratory difficulties in two-thirds of the cases. The use of mechanical ventilators was significantly higher in type II patients than in type III patients. Genetically, all patients exhibited deletions in exons 7 and 8 of *SMN1*. Among the 27 patients analyzed for *SMN2* copy numbers (9 type II and 18 type III), all type II patients had three copies, while in type III, 47% had three copies and 53% had four copies. These clinical and genetic spectra were consistent with those reported in previous studies.[1,5,16]

Our study showed prolonged diagnostic delays compared with previous studies.[1,9,12,13] Upon analyzing the diagnosis times, our study demonstrated an increased age at symptom onset and diagnosis in recently diagnosed patients. Conversely, a previous large-scale study showed that the more recent the diagnosis, the younger the diagnosis age for types I and II and the

older the diagnosis age for type III.[1] We believe that the differences between our findings and previous results may be attributed to several factors. First, previous studies focused on pediatric patients, whereas our study focused on adult patients in the neurology department. Neurologists primarily treat adult patients, which means that patients with SMA diagnosed by neurologists frequently present with atypical phenotypes or present at a later age of symptom onset. Second, advances in diagnostic technology and treatment have played key roles. Initially (1996–2004), genetic testing for *SMN1* was challenging in Korea and was restricted to patients exhibiting typical clinical features. Subsequently, *SMN1* genetic testing has become more widespread, and the interest in SMA among both patients and clinicians has surged since the launch of nusinersen in Korea in 2019. Consequently, the number of newly diagnosed patients with SMA with late clinical onset or atypical presentation may have increased.

Our study highlighted that Korean patients with SMA had numerous clinic visits before diagnosis, irrespective of subtype, age at symptom onset, or age at diagnosis. This trend, as reported in previous studies,[9,12,17,18] was also observed in the present study. This may be associated with the following factors. First, our study was conducted mainly in adult patients with type III SMA. A previous study also showed that type III patients had more visits to health facilities before their diagnosis compared to type II patients.[9] Second, until the recent development of excellent treatments, some clinicians and patients believed that genetic neuromuscular diseases were incurable and overlooked the importance of accurate diagnosis. The third factor may be Korea's nationwide single health insurance system, which offers low diagnostic costs and easy access to medical institutions.

The most common initial symptoms were delayed development of sitting posture in type II and unsteady ambulation in type III, consistent with a previous study.[1] Nevertheless, needle EMG, used in approximately 90% of all patients, is the most frequently employed evaluation test prior to diagnosis. This percentage was notably higher than that reported in a previous study.[1] This elevated usage can be attributed to our predominantly adult population. Needle EMG is highly valuable in the differential diagnosis of SMA and muscular dystrophy.[19,20] However, it poses challenges when performed on uncooperative children but is more manageable in adolescents and adults.

Our study had several limitations. First, this was a single-center retrospective study with a limited number of patients. Secondly, there was a recall bias regarding the age of symptom onset. Third, during the 25-year study period, technology and treatment protocols improved in the medical field. However, as SMA is a rare disease and there are limited studies on its diagnostic delay, especially in adults, we believe that our study is clinically meaningful.

In conclusion, our investigation represents the first examination of the diagnostic journey in Korean patients with SMA. As treatments for SMA evolve, the significance of an accurate diagnosis has increased, highlighting the importance of reviewing the diagnostic advancements made thus far.

## DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon request from the corresponding author.

## ACKNOWLEDGEMENTS

This study was supported by the Basic Science Research Program of the National Research Foundation of Korea (NRF), funded by the Ministry of Education [Grant No. RS-2023-00242210].

## AUTHOR CONTRIBUTIONS

Conceptualization: Young-Chul Choi and Hyung Jun Park. Data curation: Soo-Hyun Kim, Chung Seok Lee, Sung Rok Lee, and Hyung Jun Park. Formal analysis: Soo-Hyun Kim and Hyung Jun Park. Funding acquisition: Young-Chul Choi and Hyung Jun Park. Investigation: Soo-Hyun Kim, Chung Seok Lee, Sung Rok Lee, and Hyung Jun Park. Methodology: Soo-Hyun Kim, Young-Chul Choi, and Hyung Jun Park. Project administration: Young-Chul Choi and Hyung Jun Park. Resources: Seung Woo Kim, Ha Young Shin, Soo-Hyun Kim, and Hyung Jun Park. Software: Soo-Hyun Kim and Hyung Jun Park. Supervision: Young-Chul Choi and Hyung Jun Park. Validation: Seung Woo Kim, Ha Young Shin, Young-Chul Choi, and Hyung Jun Park. Visualization: Soo-Hyun Kim and Hyung Jun Park. Writing—original draft: Soo-Hyun Kim and Hyung Jun Park. Writing—review & editing: Soo-Hyun Kim and Hyung Jun Park. Approval of final manuscript: all authors.

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