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Original Article

Common complications in spinal muscular atrophy (SMA) type 1 after nusinersen treatment

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ABSTRACT

Background. Spinal muscular atrophy (SMA) is an inherited disease with progressive muscle weakness and atrophy. Despite the new treatments developed recently, primary and secondary effects of muscle weakness in patients with SMA cause mortality and morbidity. The aim of this study is to identify common problems in the follow-up of patients after new treatment modalities and to examine the difficulties in management of these problems.

Methods. The study included 16 patients diagnosed with SMA type 1 according to clinical findings and genetic results between 2017 and 2022. The patients were divided into two groups as living and deceased, and complications were examined and compared between the groups.

Results. The patients comprised 8 (50%) females and 8 (50%) males with a median age at diagnosis of 3 months. The patients had a history of gastrointestinal problems, orthopedic problems, infection and sepsis, and especially respiratory distress. Death occurred in 8 (50%) patients during follow-up (median age 38 months). Mortality was higher in patients who needed tracheostomy and had gastroesophageal reflux. The survival rate was better in patients who received more nusinersen treatment and had a higher CHOP-INTEND score.

Conclusions. Despite new-generation treatments for SMA type 1, morbidity and mortality rates remain very high. As the survival rate in SMA type 1 increases, the incidence of complications similar to those frequently seen in SMA type 2 and type 3 patients also increases. The follow-up and treatment of patients with SMA should be undertaken by a multidisciplinary team.

Key words: Spinal muscular atrophy type 1, mortality, morbidity, nusinersen, *SMN1*.

Spinal muscular atrophy (SMA) is an inherited disease with progressive muscle weakness and atrophy with degeneration of spinal anterior horn cells and destruction of alpha motor neuron cells.[1] The incidence of SMA ranges from 4 to 10 per 100,000 live births.[2,3] 95% of the cases result from a homozygous deletion of *SMN1* at the chromosomal locus 5q13. Classification of SMA subtypes is determined by age at onset and clinical severity and life expectancy. An early onset of symptoms is associated with poor prognosis.[4]

In SMA type 1, limited head control, hypotonia, and areflexia are seen during the first six months of life. Type I SMA is defined as 'non-sitters'. Muscle weakness is

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the major cause of complications in SMA type 1 patients, and they are known to develop gastrointestinal, nutritional, orthopedic, and especially respiratory problems.[5] Weakness in the respiratory muscles leads to progressive respiratory failure. Feeding problems may lead to developmental delay and pulmonary problems secondary to aspiration.[6] Decreased muscle strength and impaired mobility can cause many musculoskeletal problems.[7]

Recently, promising disease-modifying therapies such as nusinersen, onasemnogene abeparvovec and risdiplam have been developed for patients with SMA.[8,9] At present, nusinersen is currently the only treatment option approved for SMA and reimbursed by the health authorities in Türkiye. Before the era of these new-generation treatments, most SMA type 1 patients died of respiratory failure under the age of two years.[1]

Despite newly developed treatments, the primary and secondary effects of muscle weakness in patients with SMA cause morbidity and mortality. The management of these complications has a direct effect on morbidity and mortality.[10,11]

The aim of this study was to review the problems that may be seen in the follow-up of SMA type 1 patients after nusinersen, one of the new-generation therapies, and to examine the difficulties encountered in the management of these problems.

Materials and Methods

The files of 22 patients diagnosed with SMA type 1 between 2017 and 2022 were retrospectively analyzed. Three patients who received onasemnogene abeparvovecalan treatment and three patients who did not receive nusinersen treatment were excluded from the study. A total of 16 patients with SMA type 1 who received at least four loading doses of nusinersen were included in the study. The diagnosis of SMA type 1 was made according to clinical findings and genetic tests.[1,4] All patients presented with limited head control, hypotonia, and areflexia in the first six months of life. In genetic tests, homozygous deletion in the *SMN1* gene and two copies of the *SMN2* gene were observed in all patients.

Nusinersen is an antisense oligonucleotide against *SMN2*.[12] It is currently the only treatment option for the treatment of SMA patients in Türkiye, which is approved and reimbursed by the health authorities. Nusinersen was administered to patients as a maintenance dose every four months following the first four loading doses (day 0, day 14, day 28 and day 63).[13] Intrathecal treatment administration was performed by a pediatric neurologist. No administration-related side-effects were observed in patients.

The patients were evaluated with respect to age, gender, medical history and family history, respiratory problems, gastrointestinal problems, orthopedic problems, number and duration of hospitalization, use and dose of nusinersen, and current Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores. In patients older than two years, the Hammersmith Functional Motor Scale Extended (HMFSE) test was used in addition to the CHOP-INTEND score for evaluation. The CHOP-INTEND and HMFSE tests were performed before each nusinersen treatment by the physiotherapist authorized to perform the tests at our neuromuscular center. Approval was obtained from the Turkish Medicines and Medical Devices Agency before each dose of nusinersen with the results of CHOP-INTEND and HMFSE tests.

Our neuromuscular center is one of four reference centers in Izmir province authorized to apply nusinersen. In our center, SMA patients are followed up and treated with a multidisciplinary approach in neurological, physical, cardiac, respiratory and gastrointestinal aspects.

The patients were divided into two groups of living and deceased patients. Student's

t-test (Mann-Whitney U if non-parametric), chi-square, or Fisher's exact test were used to evaluate whether the data of the living and deceased patient groups differed.

Approval for the study was obtained from the Non-Interventional Research Ethics Committee of Tepecik Training and Research Hospital (decision no: 2023/04-23, dated: 03/05/2023). Family consent was waived because the study was a retrospective study.

Results

The study included 16 patients diagnosed with SMA type 1, comprising eight (50%) females and eight (50%) males with a mean age of 34.9±24.1 months (median 38 months). The median age at diagnosis was 3 months (min: 1 month – max: 7 months). Consanguineous marriage was present in eight (50%) patients. There was a history of SMA in the cousins of three (18.8%) patients. No patient with a family history of SMA was diagnosed by early screening.

When the medical history was analyzed, four (25%) patients had a history of hospitalization in the neonatal intensive care unit (NICU) with a diagnosis of transient tachypnea of the newborn thought to be related to cesarean delivery.

Complications seen in deceased and living patients are summarized in Table I. It was observed that two patients had respiratory problems during sleep, so they were monitored with non-invasive mechanic ventilation (NIV) and the respiratory problems disappeared in the 3rd month of follow-up.

There was a history of at least one hospitalization in the intensive care unit due to respiratory distress in 13 (81.3%) patients. All of the deceased patients were followed up at least once in the intensive care unit due to respiratory distress (Table I).

A history of tracheostomy was present in eight patients. All patients who underwent tracheostomy had a history of prolonged intubation in the intensive care unit. Mortality was higher in patients who underwent tracheostomy. The median month of insertion of the tracheostomy was 8 months (range: 6-9 months). The tracheostomy was closed in only one patient after 13 months because the respiratory findings improved.

The median age of death of the eight patients (50%) who died during follow-up was 38 months (range: 8–48 months).

Four patients died due to septic shock in the intensive care follow-up, and two patients died due to pneumonia. Two patients were found dead at home and the exact cause of death is unknown.

There was a history of constipation in seven (46.7%) and reflux in five (31.3%) patients. Proton pump inhibitor (PPI) treatment was given to all patients with gastroesophageal reflux (GER). It was observed that the reflux symptoms of all patients regressed after PPI treatment. All the patients with reflux were in the deceased patient group (p=0.026).

Dysphagia was present in 10 (62.5%) patients, of which four (25%) received nasogastric tube (NT) and three (18.8%) received percutaneous endoscopic gastrostomy (PEG) (Table I). Weight gain was observed to be better in the follow-up of the patients with PEG.

All the patients regularly took vitamin D and calcium supplements, vitamin D or calcium deficiency was not detected in patients. Scoliosis was detected in eight (50%) patients with a median age of 46 months (range: 21-96 months). More severe joint contractures, especially in the lower extremities, were observed in five patients (Table I).

One of the patients suffered from sudden increases and decreases in blood pressure and episodes of flushing and pallor of extremities. This condition was considered to be autonomic dysfunction since it was accompanied by sudden changes in pulse rate and could not be explained by any other cause. In one patient,

Table I. Clinical findings in SMA type 1 patients, n (%).

	Living (n=8)	Deceased (n=8)	Total (n=16)	p
Pulmonary problems				
History of hospitalization for pneumonia	7 (87.5%)	8 (100%)	15 (93.7%)	1.000
History of hospitalization in the ICU	5 (62.5%)	8 (100%)	13 (81.3%)	0.200
Tracheostomy	1 (12.5%)	7 (87.5%)	8 (50.0%)	**0.010**
Non-invasive respiratory support	2 (25.0%)	-	2 (12.5%)	0.467
Gastrointestinal complications				
Dysphagia	3 (37.5%)	7 (87.5%)	10 (62.5%)	0.119
Constipation	3 (37.5%)	4 (50.0%)	7 (43.8%)	0.619
Reflux	-	5 (62.5%)	5 (31.3%)	**0.026**
Nutrition and malnutrition				
Use of enteral nutrition	7 (87.5%)	7 (87.5%)	14 (87.5%)	1.000
Weight loss	6 (75.0%)	5 (62.5%)	11 (68.8%)	1.000
Weight less than -2 SDS	6 (75.0%)	5 (62.5%)	11 (68.8%)	1.000
Height less than - 2 SDS	6 (75.0%)	5 (62.5%)	11 (68.8%)	1.000
Use of NT	-	4 (50.0%)	4 (25.0%)	0.077
Use of PEG	1 (12.5%)	2 (25.0%)	3 (18.8%)	1.000
Orthopedic Problems				
Joint contracture	3 (37.5%)	2 (25.0%)	5 (31.3%)	1.000
Scoliosis	4 (50.0%)	5 (62.5%)	8 (50.0%)	1.000
Sepsis	1 (12.5 %)	4 (50.0%)	5 (31.3%)	0.282
Urinary tract infection	2 (25.0%)	5 (62.5%)	7 (43.8%)	0.315
Other				
Pressure ulcer	-	1 (12.5%)	1 (6.3%)	1.000
Autonomic dysfunction	-	1 (12.5%)	1 (6.3%)	1.000

ICU, intensive care unit; NT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy; SDS, standard deviation score.

bedsores were detected during long-term intensive care follow-up.

All patients presenting with fever in our center are tested for urinary tract infection. Urinary system infection was detected in seven (43.8%) patients in this study. Although not statistically significant, a history of urinary tract infection and sepsis was observed more frequently in patients who died (p=0.282).

The comparisons of the number and duration of follow-ups and treatment of the living and deceased patients are summarized in Table II. Mortality was found to be higher in patients who needed tracheostomy and had gastroesophageal reflux. The survival rate was better in patients who received more nusinersen and had a higher CHOP-INTEND score and HMFSE (Table II).

Discussion

In SMA type 1, many complications develop as a result of progressive muscle weakness. However, since the introduction of new promising treatments such as nusinersen, life expectancy has increased.[14,15] Therefore, prolonged life expectancy leads to the emergence of problems similar to the complications frequently seen in SMA type 2 and type 3 patients. Since mortality is still very high in SMA type 1, correct management of these complications plays an important role in reducing morbidity and mortality. Therefore, it is of critical importance to know the complications in these patients.[16,17]

Table II. Comparisons of the number and duration of follow-ups and treatment of living and deceased patients.

	Total (n=16)	Living (n=8)	Deceased (n=8)	p-value
Female gender, n (%)	8 (50.0%)	5 (62.5%)	3 (37.5%)	0.619
Age at diagnosis, months	3	3	4	0.330
Age at onset of first symptoms, months	2	2	2.5	0.318
Follow-up period, months	38 (6-96)	32 (6-96)	38 (8-48)	0.717
First CHOP-INTEND score	18 (2-47)	18 (11-47)	16 (2-25)	0.105
Last CHOP-INTEND score	41 (19-64)	48 (29-64)	37 (19-64)	**0.071**
First HMFSE score	17.5 (2-37)	23.5 (15-37)*	5 (2-8)**	**0.025**
Last HMFSE score	19 (0-38)	25 (18-38)*	4 (0-8) **	**0.028**
Age at first nusinersen treatment, months	6 (2-30)	4 (2-30)	7 (2-30)	0.820
Number of nusinersen doses	6 (4-18)	11 (4-18)	5 (4-11)	**0.071**

Data presented as median, followed by (min-max) if available, unless otherwise specified. *(n=4), **(n=2)
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HMFSE, Hammersmith Functional Motor Scale Extended.

The aim of this study was to evaluate common problems encountered in the follow-up of patients with SMA type 1 receiving nusinersen treatment.

Pulmonary complications

Pulmonary complications are an important cause of morbidity and mortality in patients with SMA type 1.[18] Respiratory problems often result from hypoventilation, weakness in the cough reflex, and difficulty in expelling secretions. The severity of pulmonary complications is closely related to the type of SMA. All children with SMA type 1 and approximately one-third of patients with type 2 experience respiratory problems. Therefore, respiratory complications should be monitored more closely.[19,20]

Decreased hospitalisation rates after nusinersen treatment have been reported in literature[21,22], while other studies have reported no change in hospital admissions.[23]

In the current study, 15 (93.8%) patients had a history of at least one hospitalization due to respiratory distress caused by pneumonia. Of these patients, 13 (81.3%) were followed up in the intensive care unit at least once. These results indicate that further multicentre studies with larger cohorts are needed.

With the progression of the disease, NIV support at night may be required in children with respiratory distress during sleep. Ventilatory support may also be needed later in the day if daytime hypercapnia becomes a problem.[24] In addition, the benefit of early ventilatory support has been shown to improve survival and life assurance.[25] In the current study, it was observed that two patients had respiratory problems during sleep, so they were monitored with NIV and their respiratory problems disappeared in the 3rd month of follow-up.

Tracheostomy may be required in patients who cannot tolerate NIV and have prolonged intubation during intensive care admission.[26] Tracheostomy and NIV increase survival. Despite being an invasive method, tracheostomy is known to significantly reduce hospitalization rates compared with NIV.[27]

Lavie et al. reported that assisted ventilation needs remained stable after nusinersen in most patients with SMA type 1. Two of the patients in that study were reported to have died from acute respiratory failure and one patient suffered severe brain damage.[28]

Tracheostomy (due to prolonged intubation) was performed in eight (50%) patients in the current study, and of these, seven died during follow-up. These findings differed from the

literature. It was thought that the increased mortality rate in patients who underwent tracheostomy may have been due to long hospital stays in the intensive care unit and complications such as infection.

Gastrointestinal complications

Gastrointestinal complications are much more common in patients with SMA type 1 than previously thought. The most common problems are GER, delayed gastric emptying, and constipation. These complications may increase the risk of aspiration and pneumonia and cause morbidity.[29]

In a study by de-Andrés-Beltrán et al. investigating the clinical and phenotypic characteristics of SMA type 1 patients after new pharmacological treatments, 18 of 50 patients (36%) had a history of GER.[30] Similar to the literature, five (31.3%) of the current study patients had a history of GER. Gastroesophageal reflux can be treated with acid neutralisers and/or acid secretion inhibitors such as histamine blockers and PPI. In all of the current study patients, symptoms disappeared after PPI treatment.

Symptoms of gastaroinsteinal dysfunction, such as GER, constipation, delayed gastric emptying, are important determinants of morbidity and mortality.[31,32] In the current study, all the patients with GER were lost even if treated. This was attributed to possible chronic pulmonary side-effects of GER.

In 2023, Chacko et al. found abnormal swallowing characteristics in eight patients with SMA type 1 who were receiving disease-modified therapy.[33]

Unlike the literature, the rate of dysphagia in the current study was found to be 62.5%. This was attributed to the retrospective nature of the study and lacking methods such as swallowing status scale, swallow questionnaire, surface electromyography, and videofluoroscopic studies to evaluate dysphagia.

There is no consensus on when to refer patients for gastrostomy tube placement.[1] Insertion of the gastrostomy tube does not protect patients from aspiration of oropharyngeal secretions, although some studies have suggested moderate benefit from this approach.[34]

Lavie et al. showed that 94% of 20 SMA type 1 patients receiving nusinersen treatment were fed by invasive methods.[35] In the current study, this rate was lower than the literature. A NT was applied in four (25%) patients, and PEG was performed in three (18.8%) patients, and it was observed that the weight gain of the patients was better after PEG. These results once again emphasise the importance of methods such as NT and PEG.

Nutrition and malnutrition

Malnutrition is common in SMA type 1 patients. The increased risk of malnutrition in SMA patients can lead to loss of lean body mass, which can weaken the strength of already weak muscles, especially the respiratory muscles.[36,37]

Feler et al. reported that malnutrition was frequently seen in patients with SMA and that patients who were started on nusinersen therapy showed more significant improvement in nutritional status after nutritional interventions.[38] Therefore, patients should be evaluated in terms of nutrition during their follow-up, and attention should be paid to malnutrition.[39]

The literature indicates that individuals with SMA type 1 exhibit lower median weight and height.[40] Enteral nutritional supplements were administered together with the formula to 14 (87.5%) patients because they did not gain sufficient weight. In 11 patients, both weight and height percentiles were below the -2 standard deviation score (SDS) for age.

It has been shown that bone mineral density tends to decrease with advancing age in SMA patients. Therefore, patients should take adequate vitamin D supplements.[41] All the current study patients received regular vitamin

D and calcium supplements, and no vitamin D or calcium deficiency was observed in patient.

Orthopedic problems

The weakness and decreased range of motion seen in SMA type 1 results in a predisposition to numerous musculoskeletal problems.[1,42,43] Although scoliosis is mostly seen in almost all patients with SMA type 2 and type 3, data on this subject are limited in patients with type 1 diagnosis.[44] With the increase in life expectancy after new generation treatments, scoliosis has become a frequent complication in patients with SMA type 1 diagnosis.

It has been reported in the literature that the rate of scoliosis development in SMA type 1 patients receiving nusinersen treatment varies between 75% and 100%.[35,45] In the current study, scoliosis was detected in eight (50%) patients and was attributed to the limited number of cases.

The development of joint contractures due to muscle weakness and immobility is one of the most common complications in patients with SMA type 1.[46] Increased duration of immobility and loss of motor function may aid the development of contractures.[47] In the current study, joint contractures, which were more prominent especially in the lower extremities, were observed in five patients. Although there are few studies in the literature about the incidence of joint contracture after nusinersen, it is known that individual physical therapy programs and passive movement of the joints help to prevent joint contractures.[48]

Infection-related complications and mortality

The natural course of SMA type 1 is poor. Patients usually die before the age of two years.[1] In a study by Thomas et al. in 1993, the median age of death in SMA type 1 patients was seven months, while in a study by Kolb et al. in 2017 it was eight months.[49,50] Even though mortality rates due to nusinersen treatment have decreased significantly, the mortality rate remains high in patients with SMA type 1.[51]

In the current study, mortality developed during follow-up in eight (50%) patients at a median age of 38 months.

SMA type 1 is known to be a common cause of sudden infant death syndrome.[52] In this study, sudden infant death of unknown cause was recorded for two patients. In the literature, cases have been reported of symptomatic bradycardia and unexpected cardiopulmonary arrest thought to be due to autonomic involvement in patients with SMA.[53,54] In patients with no determined etiology, the possibility that the cause of sudden unexpected death was related to autonomic dysfunction was considered.

Better survival of the current study patients was associated with nusinersen treatment. When the characteristics of the living and deceased patients were compared, it was found that the surviving patients had received a greater number of nusinersen doses than the patients who died, which was consistent with the findings in literature.[55]

Weakness of pelvic muscles and sphincter defects in individuals with SMA can lead to urinary retention.[56] It is known that urinary retention and urinary catheterization increase the risk of urinary tract infections and therefore urosepsis.[57]

Literature regarding the incidence of urinary tract infection in SMA type 1 patients is sparse. However, in a study by Gök et al. it was reported that the risk of nephrolithiasis was higher in patients with SMA type 1 and urinary tract infection was observed more frequently in these patients.[58]

Urinary system infection was detected in seven (43.8%) patients included in this study. It was also observed that patients who died had a more frequent history of urinary tract infection. Although it was not statistically significant, it was thought that this may have been related to hospital-acquired and resistant infections, which increase with a prolonged length of stay in the intensive care unit.

Other

Autonomic system involvement may be seen in SMA.[59-61] Autonomic dysfunction is one of the rare complications that can be seen in patients with SMA. Varriable measurements of blood pressure and heart rate, hyperhidrosis, GER, constipation, cardiac conduction abnormalities and cold-induced vasodilation of the fingers may occur.[59,62] In the current study, sudden increases and decreases in blood pressure accompanied by flushing were observed in the follow-up of one patient.

Pressure ulcers are one of the most common problems in immobile patients. Patients with SMA are also at risk of pressure ulcers. In a multicentre study conducted in the Catalonia region, pressure ulcers were observed in 10 (26.3%) of 38 patients with SMA type 1 who did not receive treatment, whereas in the current study, only two (9%) patients had pressure ulcers.[63] The less frequent occurrence of pressure ulcers in this study was thought to be because our patients received nusinersen treatment and anti-bedsore mattresses were used in the follow-up of immobile patients.

Limitations of the study

As this study was retrospective in design, standardized methods for dysphagia assessment could not be used, also the sample included deceased patients. These prevented the application of widely accepted tools such as swallowing status scale, swallowing questionnaire, surface electromyography and videofluoroscopic methods. Similarly, measurements of mid-arm circumference and triceps skinfold to determine malnutrition were also lacking in the available data set. These limitations should be taken into account when interpreting the results of the study and it should be emphasised that more comprehensive assessment methods should be used in future studies.

Conclusion

Morbidity and mortality rates remain high in SMA type 1 patients despite new generation therapies. Follow-up and treatment processes should be managed with a multidisciplinary approach. Prediction of the natural course and risks, determination of appropriate treatment options and timely intervention are important. There is a need to understand the changes caused by new treatment regimens in patients with motor symptoms, especially scoliosis, hip dislocation, dysphagia and GER. Therefore, it is important that further large-scale and multicenter prospective studies are conducted.

Ethical approval

Approval for the study was obtained from the Non-Pharmacological Clinical Research Ethics Committee of Tepecik Training and Research Hospital (Decision no: 2023/04-23 Date: 03/05/2023) Family consent was waived because the study was a retrospective study.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: YG, FB; data collection: NOD, FB, YG, PGP; analysis and interpretation of results: YG, OB, NOD; draft manuscript preparation: MK. All authors reviewed the results and approved the final version of the manuscript

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Conflict of interest

The authors declare that there is no conflict of interest.

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