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Case Report

Long-Term Effects of Nusinersen Combined Physiotherapy in Spinal Muscular Atrophy Type 1: A Case Study

Nusinersen ile Kombine Fizyoterapinin Spinal Musküler Atrofi Tip 1'de Uzun Dönem Etkisi: Olgu Çalışması

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ABSTRACT

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder that is characterized by generalized muscle weakness. Any study does not exist showing the results of Nusinersen and physiotherapy in SMA type 1. Our case was diagnosed with SMA type 1 at the age of 3 months. At 8 months of age, Nusinersen treatment and physiotherapy were started. The motor skills were evaluated with CHOP-Intend and Hammersmith Infant Neurological Examinations-2 (HINE-2) before physiotherapy and Nusinersen treatments, and also applied before each dose of Nusinersen during 22 months. An increase of 14 and 13 points in CHOP-Intend and HINE-2 were shown from baseline to the last visit, respectively. This report revealed the improvement of motor functions of a child with SMA type 1 by the combination of physiotherapy and Nusinersen. Our study may encourage physiotherapists and physicians to long-term use of a combination of these two therapies for the aim of motor improvement in this neuromuscular disease.

Keywords: Physiotherapy, nusinersen, spinal muscular atrophy

ÖZ

Spinal musküler atrofi (SMA), genel kas zayıflığı ile karakterize otozomal resesif nöromüsküler bir hastalıktır. SMA tip 1'de Nusinersen ve fizyoterapinin sonuçlarını gösteren herhangi bir çalışma bulunmamaktadır. Olgumuza 3 aylıkken SMA tip 1 tanısı konuldu. Sekiz aylıkken, Nusinersen tedavisi ve fizyoterapi başladı. Motor becerileri, fizyoterapi ve Nusinersen tedavilerinden önce ve 22 ay boyunca da her Nusinersen dozundan önce CHOP-Intend ve Hammersmith Infant Neurological Examinations-2 (HINE-2) ile değerlendirildi. CHOP-Intend ve HINE-2'de ilk değerlendirmeden son değerlendirmeye sırasıyla 14 ve 13 puan artış gösterildi. Bu sonuç, SMA tip 1'li bir çocuğun motor fonksiyonlarının fizyoterapi ve Nusinersen kombinasyonu ile geliştiğini ortaya koydu. Çalışmamız, fizyoterapist ve hekimleri bu nöromusküler hastalıkta motor iyileştirme amacıyla bu iki tedavi kombinasyonunun uzun süreli kullanımına teşvik edebilir.

Anahtar kelimeler: Fizyoterapi, nusinersen, spinal musküler atrofi

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INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the degeneration and loss of lower motor neurons, which leads to muscle atrophy and generalized muscle weakness. The incidence of this disease is estimated to be one in 11,000 live births [1]. The disease is divided into phenotypes (types 0-4) according to the age of onset of clinical symptoms and the best motor achievement. Approximately 60% of SMA patients are born with SMA type 1 which is the most severe form following type 0. The clinical signs occur before six months of age and the lifespan is limited to two years without respiratory support. The most frequently seen clinical symptoms are severe hypotonia and weakness without head control [2,3]. Weakness is usually symmetrical and the legs are weaker than the arms. Infants with SMA type 1 are unable to sit without support and have a typical respiratory pattern called "paradoxical breathing" as a result of wasting in intercostal muscles [3,4]. SMA was an incurable disease until a few years ago, but in recent years studies on the treatment of SMA have accelerated.

The survival motor neuron (SMN) gene encodes SMN mRNA and produces the SMN protein. People have two

SMN gene forms: the survival motor neuron 1 (*SMN1*) and survival of motor neuron 2 (*SMN2*). SMA occurs as a result of a mutation or homozygous deletion in *SMN1* gene. *SMN1* is responsible for producing full length of SMN protein while SMN2 acts like the compensatory gene encoding SMN protein of which the translated protein is truncated and non-full length genome that is rapidly degraded as a result of abnormal splicing [5]. The phenotype of the disease is determined according to the SMN copy number in which the disease appears milder in patients with a high number of *SMN2* gene copies [6]. Therefore, modifying *SMN2* splicing as in nusinersen treatment could be an important treatment strategy to increase the levels of SMN protein [7].

Nusinersen is an antisense oligonucleotide drug that has been developed for SMA patients. It is designed to increase production of functional SMN protein through modifying pre-mRNA splicing of *SMN2*. The phase I and II studies of nusinersen showed that drug is safe, tolerable, and could improve motor functions especially in early period of the disease [7,8].

Musculoskeletal and functional deficits, respiratory dysfunction, feeding and swallowing problems caused by weakness are dramatically common in SMA type 1. Thus, improving functional mobility/ability by positioning, contracture management, respiratory, strengthening, and range of motion exercises is the main focus of physiotherapy for these patients [9]. It has been known that different types of aerobic training may improve the motor and pulmonary functions and quality of life of SMA type 2 and 3 patients [10-13]. Although results of combined treatment with nusinersen and physiotherapy in SMA type 1 patients have not been demonstrated in the literature so far, nusinersen treatment, alone, has been proven to be effective on motor functions of patients with SMA type 1 [7,8,14]. Therefore, in this study we aimed to determine long-term effects of combined treatment with nusinersen and physiotherapy on motor function in a patient with SMA type 1.

CASE REPORT

Our case was a female patient who was born with normal spontaneous vaginal delivery with a normal birth weight of 3,300 gr at 40th gestational week. Fifteen days after her birth, her parents noticed decreased leg movements. Thus, the pediatrician referred the parents to a pediatric neurologist at the age of 3 months with symptoms of "floppy baby syndrome." Then the case was referred for genetic consultation by pediatric neurologist. DNA analysis revealed the deletion in exon 7 in *SMN1* gene and exon 8 (*SMN1* DelE7, *SMN2* DelE8) with 2 copy numbers of *SMN2* gene indicating SMA type 1 diagnosis. There was a consanguinity between the parents, but no family history of SMA disease was detected. Her mother had 5 pregnancies including 3 deliveries and 2 abortions. Our case was the third child of the parents and the only one with SMA diagnosis. The main symptoms of the patient before treatment were hypotonia, decreased deep tendon reflexes, decreased movements of the upper and lower extremities, and inability to sit without support. At 8 months of age, nusinersen treatment and physiotherapy were started. The researchers' expectation from treatment was to reduce the patient's clinical symptoms and improve her functional status which also matched with the parents' expectations. Written and verbal consents were obtained from the family.

This study had two primary efficacy end points. The primary endpoint was the motor-milestone response, which was defined according to the results on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP Intend). CHOP Intend is a validated functional test that developed to evaluate motor skills of infants with SMA. The test consists of 16 item scale scored between 0-4 points. The total score ranges from 0 to 64 points and higher scores indicate better motor function. CHOP Intend analyses to examine strength during spontaneous, reflexive, or target-specific movement, while also examining the behavioral state of infants [15].

Secondary outcome measure of the study was The Hammersmith Infant Neurological Examination (HINE). HINE is a validated scale which contains 37 items under three sections. Section 2 is related to the motor developmental milestones which we used in current study. The total score of Section 2 of HINE (HINE-2) ranges from 0 to 26 and assesses eight motor milestone achievement as voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking. Higher scores indicate better motor function [16]. The motor skills of the case were evaluated by CHOP Intend and HINE-2 before physiotherapy and Nusinersen treatments, and also applied before each dose of Nusinersen.

Range of motion, muscle tone, head control, and deep tendon reflexes of case were also assessed before treatment and before each Nusinersen dose. In addition, the history of pulmonary infection of the case and side effects of drug which was seen by the parents were asked.

Interventions

Nusinersen treatment has been started when the case was at 8 months of age within Expanded Access Programme. Nusinersen were delivered intrathecal injection by a pediatric neurologist on treatment days 1, 15, 29, 64, 183, 302, 421, 540, and 659. First four doses of Nusinersen were considered as loading doses [14].

Physiotherapy training started at the same time with first dose of Nusinersen. Physiotherapy session was performed by a physiotherapist, who has a 3-year experience in neuromuscular diseases, for one hour a day, 2 days a week during 22 months.

The physiotherapy session included following activity/exercises which were performed within a play activity suitable for the age of the case with encouragement of the therapist:

- Active limb movements followed initial active-assistive/passive normal range of motion exercises as the functional skills of the case improved.

- Assisted kicking to strengthen the leg muscles,

- Reaching to the objects to strengthen the arms in prone and supported sitting positions.

- Rolling from supine to prone and weight bearing in supine/prone/sitting positions.

- The case was also encouraged to transfer weight on forearms in prone.

- Activities to facilitate head control in supine/prone/sitting positions and weight bearing in supported sitting positions to strengthen neck and upper trunk extensor muscles on an exercise ball.

- Standing activity with a trunk-hip-knee-ankle-foot-orthosis (THKAFO) after gaining of full head control and independent sitting.

- Functional reaching and weight bearing exercises while standing with THKAFO.

Same activities/exercises were also taught to parents and were administered on remaining days of the week during 22 months. Parents were informed about appropriate positioning and carrying posture of the case. Postural drainage techniques were also taught to parents and was asked to practice at home each day.

The sustainability of the home program was achieved by regular interviews with the parents via calling or online face-to-face interview.

The case had a head circumference of 40 cm and body mass index (BMI) of 15.6kg/cm^2 before treatment. After 22 months, head circumference and BMI developed to 48 cm and 15.5 kg/cm^2, respectively. In physical examination, a contracture or scoliosis was not observed during treatment. The case had head control when held upright, but poor head control during traction in supine position before treatment. The case achieved head control in supine position at the age of 12 months with treatments. Sitting without support and head control from full head flexion to extension in sitting position were also accomplished during the treatment with Nusinersen and physiotherapy. In addition, she was able to roll from supine to prone and from prone to supine, and able to stand with the assistance of THKAFO after the treatment.

According to CHOP Intend score, motor function showed an increase of 11 points from baseline to the end of loading dose (a total of 4 doses Nusinersen treatment), and increase of 14 points from baseline to the last visit. In the secondary outcome measure, HINE, an increase of 2 points was observed from baseline to the end of loading dose, and an increase of 13 points from baseline to the last visit. Scores of Chop Intend and HINE according to baseline, after loading doses and last visit were shown in Figure 1.

After 8th dose of Nusinersen, a swallowing examination with videofluoroscopy was performed after a lung infection at 35 months, and the assessment revealed that the case had aspiration in liquid and viscous foods, and had no coughing response. Then the case has been started to be fed with nasogastric tube after aspiration was detected. Although she had five lung infection histories during the treatment course of 22 months, she did not need invasive or noninvasive respiratory support.

DISCUSSION

In this case report, long term effect of Nusinersen combined physiotherapy on motor functions were examined in a patient with SMA type 1. The treatment prevented the development of contracture and scoliosis, while the case gained ability to roll, full head control, sitting without support, and full range of active movement in upper extremity. She was also able to stand with an orthotic device. Despite all these improvements, swallowing and respiratory problems were detected after the 22 months treatment.

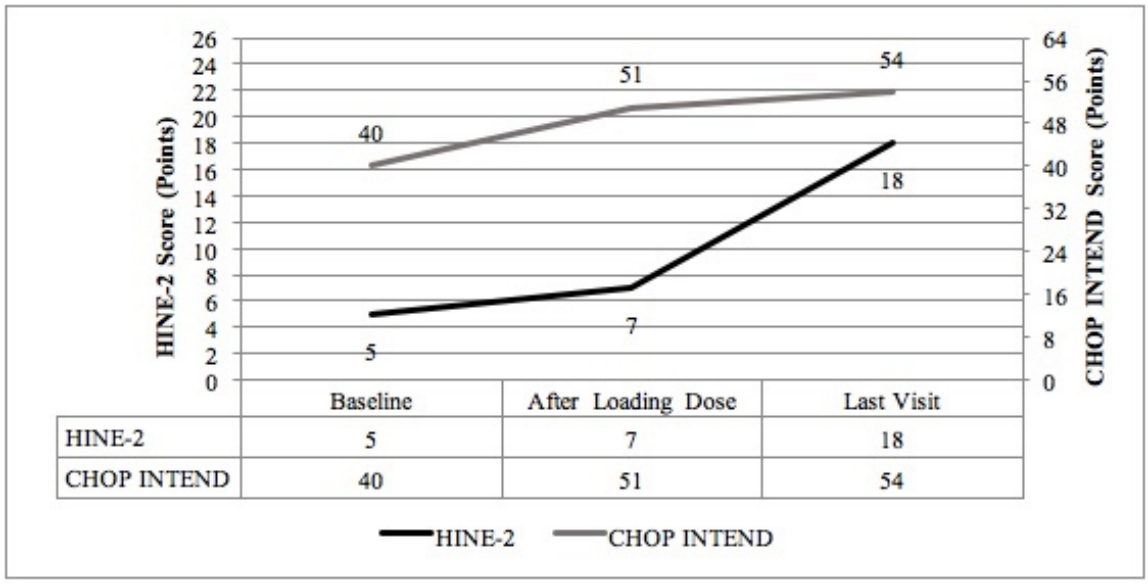

Figure 1. CHOP Intend and HINE-2 scores among the treatment process

CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE-2: Hammersmith Infant Neurological Examinations-2

A 40-point CHOP Intention score was reported to be rare in SMA type 1 patients with 2 SMN copies [17,18]. Our case had a CHOP Intend score of 40 points even before starting Nusinersen and exercise therapy and at 8 months of age, and the patient was able to maintain head control for a short time in sitting position. For this reason, our patient may be one of the rare cases with SMA type 1 diagnosis. Although Nusinersen is known to be effective even in later-onset SMA patients, we observed that regular physical therapy sessions besides Nusinersen increased patients' motor functions and protected respiratory functions [19].

Although there are studies on the efficacy of Nusinersen and exercise treatment in literature, separately, within our knowledge, there is no study investigated the long-term effect of Nusinersen combined physiotherapy in patients with SMA. In a study which examined the efficacy of Nusinersen treatment, the mean increase in CHOP Intend score was 9 points, and the mean increase in HINE score was 1.4 after loading dose. In current study, the increase in CHOP Intend and HINE scores after loading dose was found to be higher than the study of Pechmann et al. [20]. Although the authors stated that physiotherapy was performed to the majority of their patients, the therapy procedure or techniques used were not clearly explained as well as the intensity, and the type of exercise given [15]. The higher motor improvement in our case may be due to the function-targeted therapy approach with functional activity and exercises, the frequency of the sessions, regular follow-ups besides long-term Nusinersen treatment, and the initial motor ability of the case.

In the study of Nusinersen phase 2 which included subjects with 3 SMN copies, patients were reported to receive a total of 2-9 doses with 6 mg or 12 mg Nusinersen. While the mean increase in CHOP Intend score was 11.5, the mean increase in CHOP Intend score who received 12 mg was declared to be 15.2 in this study [8]. Taking into account that our case had 2 SMN copies and received 12 mg dose, the higher increase in the mentioned study might origin from the genetic feature of the patients (3 SMN copies). Considering the mean decrease of 1.27 points in CHOP Intend scores of patients with SMA per year in the natural history of the disease, the Nusinersen combined physiotherapy achieved 14 points increase which gave rise to the significant efficacy of this combined therapy on motor improvement [18].

According to the secondary outcome measure of this study, HINE, a noteworthy increase up to 2.5 times was observed from the end of loading dose to the last visit. Improvement of two or more levels on at least one category were observed in most of the participants in Phase 2 study, while there was an improvement of two

or more levels in 4 motor milestone categories in our case [8]. It has been known that SMA type 1 patients can never achieve unsupported sitting in the natural history of the disease. Therefore, the development in our case as sitting without support and standing by holding the bars with THKAFO are promising for the efficacy of the combination of physiotherapy and Nusinersen treatments on better motor function in patients with SMA type 1.

In studies related to the effectiveness of exercise in SMA type 2 and type 3 patients, an increase in the motor functions of the patients was reported [10,11,21]. However in a study which the effect of cycling exercise was investigated in patients with SMA type 2, it was reported that SMN gene expression did not increase, but the motor performances of the patients increased [9,13]. Although the importance of physiotherapy is emphasized in care standards in patients with SMA, there is no study showing its effectiveness in SMA type 1 [4].

In current study, the physiotherapy sessions were planned to support patient to achieve motor skills considering the motor developmental milestones of an infant. Thus, according to the results, it can be stated that the activities/exercises which were applied keeping in mind the functional competence of a patient with SMA may contribute to the positive effects of Nusinersen treatment, and accelerate motor function development of patients. Besides, the importance of secretion clearance techniques such as postural drainage which are known to be crucial for the rehabilitation programmes of SMA patients, revealed one more time to maintain respiratory function, and prevent invasive or noninvasive respiratory support.

However, in this case, despite the improvements in motor development and respiration without an invasive/noninvasive ventilation, pulmonary infections and feeding with nasogastric tube are quite remarkable problems still. Despite all the advances in the treatment of SMA patients including Nusinersen treatment and physiotherapy, and in care standards, aspiration is still a matter that should be focused on seriously, indicating the importance of detection the early symptoms of swallowing problems.

Informed Consent: Written and verbal consents were obtained from the family.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: G.A.Y., Concept: G.A.Y., N.B., A.A.K., Ö.Y., Design: G.A.Y., A.A.K., Ö.Y., Data Collection and/or Processing: G.A.Y., F.U., Analysis and/or Interpretation: G.A.Y., N.B., İ.A.G., Ö.Y., Literature Search: G.A.Y., Writing: G.A.Y., İ.A.G., Ö.Y.

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