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Short communication

# The outcome of two SMA cases treated with nusinersen at seven hours and at three days of life: the earliest ever

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ABSTRACT

New molecular therapies are available for the treatment of spinal muscular atrophy (SMA) but early intervention is required. We report two cases that were diagnosed prenatally, where treatment with nusinersen was initiated within 7 h and three days respectively. The children were followed up for 13 months and almost six years respectively. Both children have developed within entirely normal centiles, indicating that initiating treatment immediately after birth, as in these cases, is essential for a good outcome.



## 1. Introduction

Early diagnosis is essential in spinal muscular atrophy. By the end of 2016, two alternative therapies had been developed and approved sequentially over a three- to four-year period: nusinersen, an intrathecally administered antisense oligonucleotide molecule to promote the production of a full-length transcript from the homologous gene SMN2 [1], and an AAV9 virus-based SMN1 gene replacement therapy [2]. However, treating SMA children by such means was never free of concerns, leading to raised eyebrows soon after wide clinical application. Antisense oligonucleotide therapy in SMA, nusinersen, has already been administered to more than 12,000 cases globally within a clinical study frame or at a routine treatment facility, and similarly gene therapy in over 900 cases [3,4]. Current common sense tells us to start very early in the course of the disease; ideally at the pre-symptomatic phase [5] or, if not, before three months of age or at latest by six months in SMA I [1]. There is also another molecule at hand, risdiplam, which is not an antisense oligonucleotide but an orally administered SMN splicing modifier small molecule [6]; however, the results of its administration before the age of two months are still awaited.

Neonatal screening programs and antenatal tests have recently been implemented, and these are on the rise [7]. In this report, we describe two infants with SMA whom we were able to treat at seven hours and three days of life.

## 2. Case 1

This boy was the third child born to first-cousin parents at term after an uneventful pregnancy. Their first and second children had died at two months and six months respectively, due to SMA type 1. He was also diagnosed with SMA type 1 prenatally at gestational age three months, with a homozygous deletion of the SMN 1 gene and two copies of the SMN 2 gene. The parents decided to continue the pregnancy. At birth, he weighed 3600 g (50–90 p). On neurological examination on day 1 he was alert; spontaneous limb movements were present with semiflexor arms, hips abducted and legs partially flexed position, and normal tone. However, deep tendon reflexes (DTRs) were absent. The absence of DTRs is an early sign of SMA type 1 in the neonatal period, even before the manifestation of hypotonia and muscle weakness. After rapid approval from the health authorities locally, treatment with nusinersen was initiated at seven hours postnatally and continued according to the drug administration protocol.

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**Table 1**
Achievement of head control, six WHO gross motor milestones and CMAP findings.

| | Case 1<br>age in months | Case 2<br>age in months |
|---|---|---|
| **Head control** | 3 | 2 |
| **Sitting without support** | 7½ | 6 |
| **Hands & knees crawling** | 10 | 8 |
| **Standing with assistance** | 11 | 11 |
| **Walking with assistance** | 12 | 13 |
| **Standing alone** | 12 | 13 |
| **Walking alone** | - | 14 |
| **CMAP (from right tibialis anterior)** | 3,6 mV at 12 months | 1,30 mV at 54 months |

CMAP-compound muscle action potentials, mV-millivolts

Neurological examination at 40 days was completely normal with the presence of DTRs. Head control was achieved at three months of age, and he could sit unsupported at 7½ months. At ten months of age his CHOP-INTEND score was 54. He is continuing to achieve motor milestones at a normal pace. He has never been hospitalized for respiratory infection, and has never had feeding difficulties. He has followed a standard growth curve within the 75–90p. Electromyography performed at 11½ months was normal. Sensory nerve action potentials (on the right side) were in the sural nerve 16 μV, radial nerve 3.8 μV, and median nerve 25.9 μV. Compound muscle action potentials (CMAP) were in the right anterior tibialis 3.6 mV, and in the right abductor digiti minimi 3.8 mV. On his last visit, the day of his first birthday, his neurological status was again completely normal with the presence of DTRs and normal tone. At that time, he weighed 11 kg (50–75p), and his height was 77 cm (25–50p) with a head circumference of 46.5 cm (25–50p). He could stand with support and bear weight on his legs. He uttered his first words. He walked independently at 13 months.

## 3. Case 2

This baby girl was diagnosed prenatally at 11 weeks based on the family history. Her 6-year-old sister had SMA2 (sitter). They both had a deletion of exons 7 and 8 of the *SMN1* gene shown by the standard MLPA test. The *SMN2* copy number was 3. In the autumn of 2015, we invited the family to take part in the already started NURTURE trial, which was designed exclusively for asymptomatic newborns with SMA (three *SMN2* copies included). After parents' approval and consent, the child was delivered by an uneventful cesarean section at 39 weeks. Her birth weight was 3.6 kg. She received her first dose of nusinersen when she was three days old and she has never missed a dosage. This girl has had a remarkable evolution. When examined at 700 days, she had already reached the maximum score of 64 on the CHOP-INTEND test. She has consistently demonstrated normal results on physical and neurological examination, with preserved deep tendon reflexes. No scoliosis, contractures or any deformity was detected on physical examination. She runs perfectly, matching her peers. On day 1849 (4½ years old) her scores were: 6 min. Walk Test 329 m; Hammersmith Functional Motor Scale- 65/66, WHO Motor Milestones total score; Dual-Energy X-Ray Absorptiometry normal for the age; sensory nerve action potentials (on the right side) sural 13 μV, radial 25 μV, ulnar 22,7 μV; and CMAP from right anterior tibialis 1.30 mV. This girl is still following the NURTURE protocol. Achievement of head control, six WHO gross motor milestones and electrophysiology test results of the cases are summarized in Table 1.

## 4. Discussion

Considering that SMA is unique in its character, the spontaneous mutation rate is very low, at around 2%. The estimated incidence is 1 in 11,000 births, with a carrier frequency of 1 in 40 to 1 in 67 people; now, rapid-action alternatives and approaches have become daily conversations [8,9]. The first is routine carrier screening for SMA in the general population because there is a high carrier frequency. The main purpose of genetic screening tests is to allow couples to discuss the possible outcomes and choices openly, and jointly agree on a means of prevention. In some cultural groups for whom radical solutions are not acceptable, premarital screening has been used to determine compatibility [10]. Secondly, newborn screening can be implemented if there is a willingness by the health authorities and adequate infrastructure in the given country [11]. In the developed world, newborn screening programs are becoming implemented as routine. We accept this as an important health provision which is supported by the results of this report with the children's excellent evolution. The treatment options for effected babies should be discussed with the family in depth, and naturally this has to be done at a very early stage, preferably not beyond the newborn period. To our knowledge, our infants were the earliest ever treated SMA cases. They have followed normal developmental milestones. Initially, the male infant (Case 1) had diminished DTRs soon after birth; however, these were regained within 40 days, after the 4 loading doses of the drug. The girl (Case 2) is currently approaching 6 years of age, with normal motor and mental function. She is a preschooler, now carrying her bag and fully active. She has three copies of the SMN2 gene, which can be considered a modifying factor. Infant 1 has only two copies of the SMN2 gene with a history of sibling losses. We will continue to observe their outcome and evolution.

## Declaration of Competing Interest

NONE

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