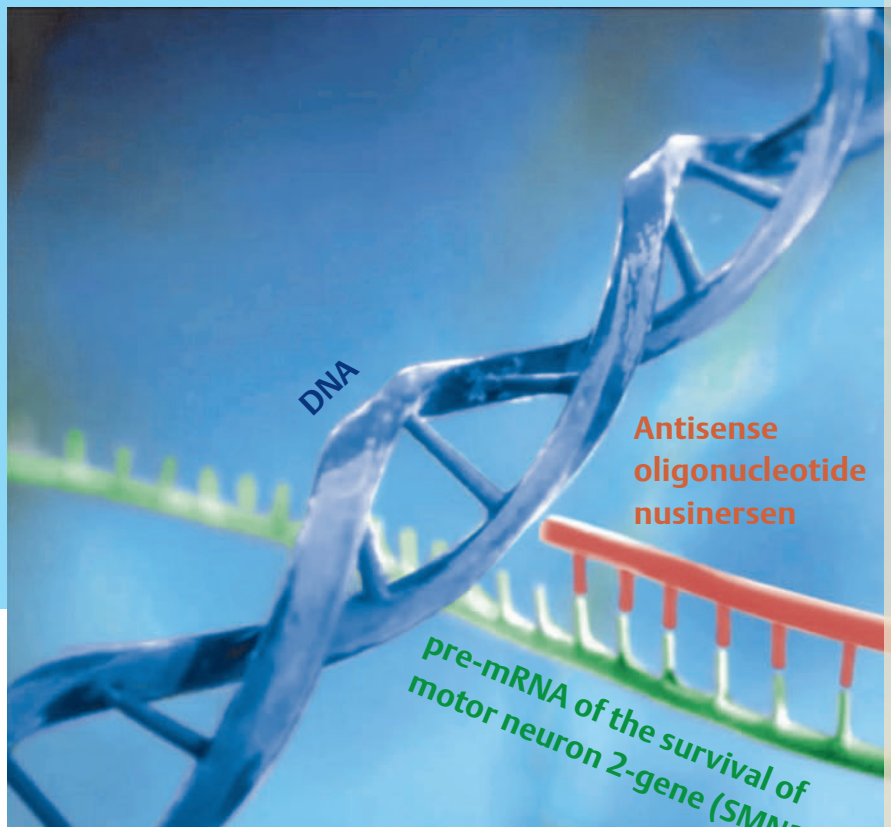
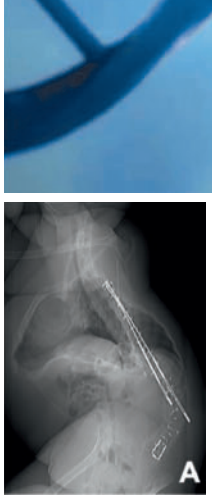
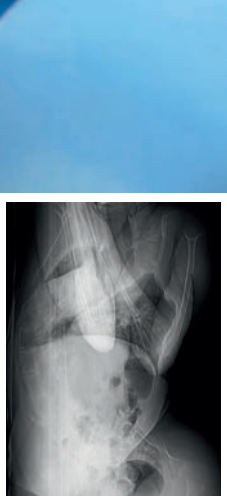
Case Report

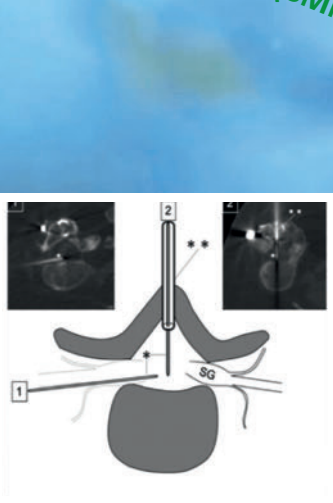


Nusinersen in the treatment of 5q spinal muscular atrophy

Effective therapy for patients in all age groups







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Case Report
Nusinersen in the treatment of 5q spinal muscular atrophy
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Thieme

Case Report

Prof. Dr. med.
Marcus Deschauer

5q spinal muscular atrophy: Nusinersen has proved effective in a wide range of treatment situations

In the past we were unable to offer patients presenting with the serious diagnosis of "spinal muscular atrophy" any causally effective treatment. Left untreated, the genetic neurodegenerative disease causes advancing atrophic paresis with progressive loss of motor function, ultimately leading to respiratory insufficiency and premature death. With an incidence of approximately 1: 8000 newborn infants, SMA is a rare disease. But we should not be fooled by the low prevalence: SMA is the most common genetic cause of death in infants and young children. In 95 % of patients there is a genetic defect in the survival of motor neuron gene 1 on the long arm of chromosome 5 (5q). The disease is then referred to as 5q-SMA. In the most severe, infantile course of the disease, without constant ventilation, children with SMA usually die before they reach the age of 2. With the marketing authorization of the splicing modulator nusinersen (Spinraza®) in mid-2017, we now have a highly effective and well-tolerated therapy strategy at our disposal which targets the pathogenesis of 5q-SMA and enables improved motor development and longer survival without permanent ventilation in infants, young children, adolescents and even adult patients. To date, more than 10,000 patients have been treated with the active substance worldwide [1]. The following case studies illustrate that the promising study data are confirmed in everyday clinical practice. With this treatment, presymptomatic infants and young children have the opportunity to reach new and recover lost milestones in their motor development. Improvements in motor function can also be achieved with nusinersen in challenging treatment situations, such as in older patients who have been living with 5q-SMA for decades and who present with severe physical disability. Even in complex spinal anatomies, such as severe scoliosis and realignment surgery with metal implants, the intrathecal administration of nusinersen is generally successful, although treatment does require special management, depending on the form of the disease. As one of the following cases shows, the support of an experienced neuroradiologist is recommended. To ensure the best possible benefits of the therapeutic potential of nusinersen offered by early diagnosis, a genetic test should be carried out as soon as the suspicion of SMA is raised.

Thieme

Nusinersen addresses a medical shortfall in the treatment of spinal muscular atrophy

SUMMARY

Due to a mutation in the SMN1 gene on chromosome 5, in 5q-SMA there is a deficiency in the survival of motor neuron protein (SMA) which is essential for motor neurons. This leads to a degeneration of the 2nd motor neuron and progressive weakness and atrophy of the affected muscles.

The targeted splicing modulator nusinersen (Spinraza®), an antisense oligonucleotide that binds to the SMN2-RNA, leads to increased production of functional SMN protein. This stabilizes the disease and improves muscle function.

5q-SMA is a rare neurodegenerative disease, which is severely debilitating and life-limiting. The deficiency in functional SMN protein leads to a progressive decline in the motor neurons in the bone marrow (2nd motor neuron) and thus loss of important motor functions. SMN protein deficiency is due to an autosomal recessive congenital homozygous deletion (or in rare cases due to point mutations) in the SMN1 gene on chromosome 5. As well as the SMN1 gene, the human genome has one or more similar but not identical genetic copies of the SMN2 gene. Due to this base exchange (C to T transition) in exon 7, there is a transcription error (splicing defect). Exon 7 is excluded in transcription and so most of the SMN protein (SMN7) coded by the SMM2 gene is shortened, dysfunctional and unstable [2].

Nusinersen increases the natural production of SMN protein

Approved in May 2017, the antisense oligonucleotide (ASO) nusinersen was the first causally effective and approved disease-modifying therapy available in the European Union for the treatment of all forms of 5q-SMA [3]. ASOs are short, synthetic, single-strand nucleic acids. Nusinersen uses complementary base pairing to bind to intron 7 on the pre-mRNA of SMN2 (▶ **Fig. 1**). This corrects the splicing error so that more complete and functional SMN protein can be synthesized during translation [4]. As ASOs cannot cross the blood-brain barrier, nusinersen (12 mg/5 ml) is injected intrathecally by lumbar puncture into the fluid-filled space of the spine [3]. The active substance is administered by intrathecal injection, which allows it to intervene in the central nervous system with high spec-

▶ **Fig. 1** Nusinersen is an antisense oligonucleotide and as a splicing modulator it intervenes in the processes of the SMN2 gene and increases the production of functional SMN protein.

▶ **Tab. 1** Typical symptoms of SMA [1, 2].

Symptoms
Main symptoms
• Hypotonia with symmetrical and usually proximal muscle weakness (especially in the hip and shoulder muscles)
• Increasing muscle loss (atrophy) accompanied by muscle weakness and paresis
• Reduced muscle tone in infants (floppy infant syndrome)
• Lower limbs more severely affected than upper limbs
• Reduction in or absence of muscle reflexes
Symptoms of muscular hypotonia
• Reduced mobility: Inability to run, altered gait
• Difficulties standing up from low seating and climbing stairs
• Difficulties raising the arms and transporting objects
• In severe cases, patients require a wheelchair
Other symptoms associated with SMA
• Skeletal defects: Scoliosis, hip luxation, joint contractures
• Respiratory insufficiency
• Difficulties chewing and swallowing
• Fatigue
• Tremor in the hands
• Tongue fasciculations

ificity, interrupting the disease mechanism and with a targeted efficacy. Its effect is thereby reversible and so there can be a positive intervention in the progression of SMA without affecting the genetic material or modifying it by gene technology [5]. Treatment starts with 4 loading doses in the first 2 months on days 0, 14, 28 and 63; a maintenance dose is then administered every 4 months [3].

Serious disease with heterogeneous symptoms

SMA patients develop progressive muscle weakness and atrophy mainly affecting the proximal extremities along with complex concomitant symptoms, particularly respiratory and orthopedic complications (▶ **Tab. 1**) [6, 7]. The clinical symptoms of SMA vary from one person to the next. Generally, 5q-SMA can develop at any age. Depending on the age of the patient when symptoms start and the severity of the disease, SMA is divided into 4 types with infantile and adult onset [8]: In type I SMA (infantile SMA) symptoms emerge in the first 6 months after birth. The first signs are an absence of head control, tongue fasciculations, areflexia and swallowing and breathing problems. The infant usually will not be able to sit, stand or walk unaided.

Without ventilation, 90 % die of respiratory insufficiency before their second birthday. In type 2 the symptoms begin after the infant is 6 months old and in type 3 after the child is 18 months old; some will even have reached adolescence by the time symptoms develop. While the children may achieve some motor development milestones, they can lose these again as the disease progresses. In children and adolescents with late onset SMA, loss of motor function tends to be slower than in types 1 and 2 SMA and so these patients reach adulthood – albeit with a progressively deteriorating ability to walk and quality of life. Many patients develop pronounced scoliosis. Without specific treatment, the disease can lead to total immobility, loss of independence and the need for artificial ventilation. Type 4 is yet another form, where the disease does not manifest until adulthood, motor function is only mildly affected and patients have normal life expectancy [8]. The key therapeutic goals in SMA patients with late disease onset are to halt the progression of the disease to preserve what motor function the patient still has (so he or she can continue to work and take part in family life), to preserve quality of life and enable the patient to have a social life [9].

Proven efficacy in all age groups

In clinical trials in SMA patients in all age groups and forms of the disease, nusinersen stabilized or improved disease progression. This includes the licensing-rele-

vant, randomized, placebo-controlled phase III studies ENDEAR in infants with type 1 5q-SMA (n = 122) [5] and CHERISH in older children (2–12 years; n = 126) with later onset types 2 and 3 SMA [10] and the phase II NURTURE study in presymptomatic newborn infants (n = 25) with genetically confirmed SMA [11]. In the ENDEAR study, 51 % of infants reached the age-appropriate motor development milestones under treatment with nusinersen compared to 0 % given the placebo intervention ($p < 0.0001$) [5]. The risk of death or of requiring permanent ventilation was reduced by 47 % ($p < 0.01$) [5]. The results of the CHERISH study show that the treatment can also lead to a significant improvement in symptoms in SMA patients with later disease onset [10]. While the HFMSE (Hammersmith Functional Motor Scale Expanded) score improved by 3.9 points after 15 months, there was a 1-point deterioration in patients given the placebo intervention ($p < 0.0001$). Under treatment with nusinersen more than half of patients exhibited a ≥ 3 point improvement in the HFMSE score compared with only 1 in 5 in the control group (57.3 vs. 20.5 %). An improvement in the RULM (Revised Upper Limb Module) score which measures hand and arm function (4.2 vs. 0.5 points) was also important for the patients' activities in daily life [10]. The disease-modifying therapy with nusinersen should be initiated at an early stage, ideally before the first symptoms appear. Current interim data from the NURTURE study in newborn infants with genetically diagnosed 5q-SMA demonstrate the favorable effect on prognosis when treatment is initiated in the presymptomatic stage [11]. Treatment started in the first month after birth. When the interim analysis was performed after a median of 317 days, none of the children had died or required permanent ventilation. At the point at which healthy young children usually start to walk, some 92 % (23/25) of the children could walk with and 88 % (22/25) without assistance [11]. The efficacy of the treatment was also demonstrated in adult patients with SMA. An observational study in patients with type 3 SMA showed an 8 m increase in walking distance in the 6-minute walk test 10 months after initiating treatment in 11 patients who were able to walk [12]. Another observational study in patients with type 2 and 3 SMA showed a 3-point increase in the HFMSE score in 57 patients after 14 months of treatment [13].

Early diagnosis, interdisciplinary care

To detect SMA early on and to initiate an effective treatment it is important to recognize the symptoms and to interpret them properly (▶ **Tab. 1**). The disease is diagnosed by a genetic test, either by EDTA blood test or dried blood spot testing. Registered physicians can request dried blood spot testing free-of-charge online at www.sma-diagnostics.com or can call Archimed Life Science GmbH on 0800 4430420. To further increase the rate of early diagnosis of SMA, it makes sense to include a genetic test for SMA in newborn screenings; this idea is currently under discussion. If the result is positive, the patient should be immediately referred to a specialized center where neurologists and neuropediatricians can provide their expertise as well as pneumologists, orthopedic specialists, genetic advisers, speech therapists, ergotherapists and physiotherapists, dietitians and social workers. This ensures that the patient receives the necessary interdisciplinary care. The center should be informed when first contacted that the diagnosis is SMA. Due to its rapid progression, SMA is considered an emergency in infants and is prioritized. An up-to-date list of hospitals that offer treatment with nusinersen is available at: http://bit.ly/SMA-DGM. Biogen offers a therapy program "Strong Together" ("Gemeinsam Stark") to run alongside the treatment to provide support for patients and their families (Tel.: 0800 070 44 00, between 8 AM and 8 PM).

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Case 1

Spinal muscular atrophy: Test siblings too

SUMMARY

One year ago, a boy who was 3.5 years old at the time, was diagnosed with type III 5q spinal muscular atrophy (5q-SMA), after his younger sister had had a positive genetic test for a severe form of SMA. Directly after the diagnosis, treatment with the antisense oligonucleotide nusinersen (Spinraza®) was initiated. For 1 year the patient has been stable and is still able to walk. The case demonstrates the importance of early diagnosis and therapy and shows how important it is to consider that siblings may also have SMA.

Medical history

The boy, who is now 4.5 years old (height: 100 cm, weight: 15 kg) was diagnosed with type III SMA about 1 year ago quite by chance when he was visiting his sister, who had already been treated in the same neuromuscular center for the past 2 months. The motor development of his younger sister was unremarkable until August 2017. By this point she had reached all motor development milestones, such as crawling and sitting unaided. According to her parents, she had become less and less mobile by the age of 1 year, and wanted to be carried around a lot. They had 2 consultations with the registered pediatrician, who did not initially directly refer the child for further diagnosis. In February 2018 a genetic diagnosis of 5q-SMA type II was made. The patient was treated with nusinersen from March 2018. The treatment was started with 4 loading doses in the first 2 months (days 0, 14, 28 and 63).

The then 3.5-year-old boy accompanied his parents to the Heidelberg Center for Pediatric Medicine (Heidelberger Zentrum für Kinder- und Jugendmedizin) when they visited for his sister's treatment. In a discussion with the parents, the suspicion was voiced that the boy might also be affected. He often tripped over and had to hold the banister when climbing the stairs, according to his parents. They reported that he tired more quickly than other children his age. In the context of these symptoms he also presented to the pediatrician, but despite the fact that there was a family history, no molecular diagnostic testing was initiated. According to his parents, the boy had reached all motor development milestones at the right time, and was often ahead of his peers mentally and in his language development. The parents said they had not had an extensive genetic consultation after the sister was diagnosed with 5q-SMA. Thus, they had not been informed that there was an opportunity to also test the older brother to see if he had the disease.

Diagnosis and therapy

During the sister's visit, an extensive neurological examination was carried out where her brother's muscle tone was examined. The boy had significant proximal muscle weakness with no muscle reflexes. When climbing the stairs he had to use both hands and the banister. He did not have any other relevant comorbidities. The findings of the examination raised the suspicion that the boy may also have SMA, albeit a milder form than his sister with preserved mobility. A genetic test was immediately initiated and the result was clear: both the sister and the boy were confirmed to have homozygous deletion in the SMN1 gene on chromosome 5. This led to a diagnosis of late-onset 5q-SMA (type III) in May 2018. At this time the patient scored 50 out of 66 in the HFMSE (Hammersmith Functional Motor Scale- Expanded) scale, indicating that his motor function was still only slightly restricted. The RULM (Revised Upper Limb Module) score was 26 points (max. 37 points).

In May 2018 treatment with nusinersen was initiated once the diagnosis was confirmed. The antisense oligonucleotide is approved for all types of 5q-SMA (including the presymptomatic stage) and all ages [1]. The first intrathecal application was administered just 4 weeks after the suspected diagnosis. In accordance with the summary of product characteristics [1], the preparation was administered by lumbar puncture as an intrathecal bolus injection of the recommended standard dosage of 12 mg for 1–3 minutes. Initially the patient received 4 loading doses within 63 days (days 0, 14, 28 and 63). Since then, nusinersen has been administered only once every 4 months as a maintenance therapy.

Disease progression

Regular treatment with nusinersen has to date been able to prevent the looming and progressive loss of

CONCLUSION

The benefit of early diagnosis and early initiation of treatment is confirmed in the case presented here. Despite known family risk factors (illness of the sister) SMA was only detected by pure chance during a hospital visit.

The early diagnosis and immediate initiation of nusinersen treatment has meant that the patient, who is now almost 5 years old, is still able to walk. Nusinersen, which gained marketing authorization in May 2017, can significantly improve the progression of the disease. Early diagnosis and therapy are critical factors, especially in the forms of the disease that manifest in infants and young children and progress very rapidly. Widespread newborn screening for SMA could be beneficial moving forwards. Until that point, siblings of patients with SMA should undergo genetic testing and their parents should have a genetic consultation. SMA centers in Germany, whose addresses are available, for example, online at the Deutsche Gesellschaft für Muskelkranke e. V. (http://bit.ly/SMA-DGM) have the infrastructure required to provide multidisciplinary care.

motor function and the development milestones the boy has reached thus far. At the last assessment, the parents reported that the disease was stable, as confirmed by the regular systematic motor function tests: At the last examination in March 2019 the RULM score had improved from 26 to 35 points; the HFMSE remained stable at 50 points. Since the start of treatment the patient has not lost any further motor function. All in all, his physical endurance and resilience have improved. To date there have been no undesirable effects associated with the therapy.

Discussion

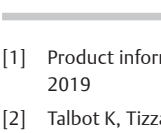
The use of nusinersen can stabilize disease progression in the early phase of 5q-SMA in patients who are only oligosymptomatic or who only have mild symptoms and can, in most cases, preserve or even improve motor function.

To date, he is still able to walk and is not depending on constant wheelchair use, in contrast to untreated patients in the past. There were no complications with the intrathecal injections. Both the boy and his younger sister tolerate the therapy very well.

Spinal muscular atrophy is a rapidly advancing neuromuscular disease, usually caused by homozygous recessive mutations in the SMN1 gene on chromosome 5q [2]. The antisense oligonucleotide nusinersen launched in Germany in July 2017 was the first approved therapy in the European Union that targets the molecular pathophysiology of 5q-SMA [1]. Nusinersen modifies the splicing process of the limited function SMN2 back-up gene, so that patients can produce larger amounts of the SMN protein which is essential for the motor neurons, despite the defect in the SMN1 gene [1].

The current interim results of the ongoing phase II NURTURE study in 25 asymptomatic newborn infants with genetic confirmation of 5q-SMA indicate that the success of treatment with nusinersen depends very much on when treatment is started [3]. In the NURTURE study, treatment started when the infants were ≤ 6 weeks old. After a median observation period of 33.9 months (max. 45.1 months) all children were still alive [3]. They reached their motor development milestones and their development was broadly age-appropriate. None of the children required permanent ventilation [3].

Authors



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Case 2

5q-SMA: Early initiation of nusinersen treatment following prenatal diagnosis

SUMMARY

5q spinal muscular atrophy (5q-SMA) is a rare, progressive neuromuscular disease and, left untreated, used to be one of the most common genetically inherited causes of death in infants and young children. If there is a positive family history, siblings should also be tested as early as possible and should receive specific treatment if 5q-SMA is identified. The following case confirms that early initiation of treatment with nusinersen enables largely normal development. The infant presented here was diagnosed prenatally; this diagnosis was confirmed postnatally.

Medical history

A patient who is now just 2 years of age, had a positive family history of 5q-SMA. In 2010 his sibling had died of SMA type 1 at the age of 8 months. After extensive genetic consultation and exploration of the risks of an invasive prenatal diagnosis, [1] the patients opted for an amniocentesis.

Prenatal diagnosis and course of the disease

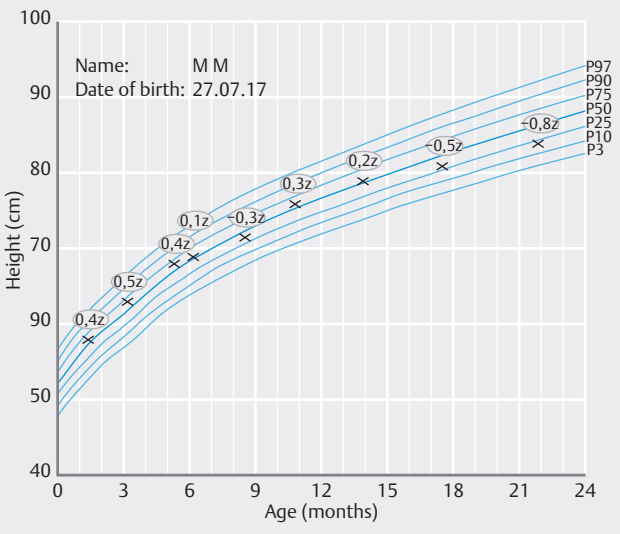
The molecular genetic findings confirmed homozygous deletions of exons 7 and 8 in gene SMN1 (survival of motor neuron 1) on chromosome 5 (5q13.2). The pregnancy was otherwise unremarkable. There were no complications during the birth by C-section or in postnatal adaptation. Slight tongue fasciculations were observed during physical examination. Otherwise, the neurological status was normal. The newborn infant had no evident signs of muscle weakness. A postnatal genetic test confirmed the initial diagnosis of type 1 5q-SMA.

Early postnatal development

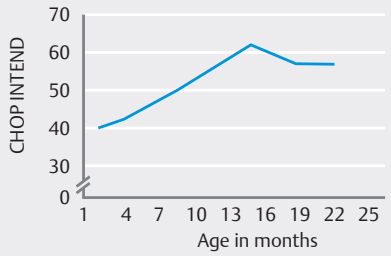
The first intrathecal administration of nusinersen was administered at the age of 2 weeks. The splicing modulator is approved for the treatment of symptomatic and presymptomatic 5q-SMA patients in all age groups [2]. At this point the boy had reduced spontaneous motor function and the first signs of proximal muscle weakness in the lower extremities. To date, a total of 9 intrathecal doses of nusinersen have been administered with no complications. The patient has been fed orally at all times. However, the now 22-month-old boy still has difficulty eating solids. His weight and height are within a normal range (▶ **Fig. 1**). At the age of 22 months he has a body mass index of 17.6 kg/m^2, placing him in the 76th percentile. Ventilation was not required at any point. At the age of 6 months he was suspected to have the onset of a secondary REM-associated hypoventilation syndrome. However, at the age of 13 months, a relevant sleep-related breathing disorder was ruled out. He has not had any severe respiratory infections to date.

Milestones in early childhood development

Initially, under regular treatment with nusinersen, motor development milestones were reached at the appropriate age by and large, but later on there was a



▶ **Fig. 1** Height development in a patient with 5q-SMA under treatment with nusinersen.



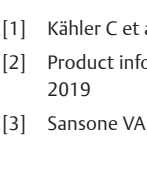
▶ **Fig. 2** Development of CHOP Intend score under treatment with nusinersen.

delay. The infant was able to turn on his side at the age of 4 months, consistent with healthy development. He was also able to hold his head in all positions from the age of 5 months. He could flip over from his back to his front and back at the age of 8 months (> usually achieved at 4–6 months) and vertically raise his legs in a supine position at the age of 8 months (> usually achieved at approximately 3 months). At the age of 11 months he was able to sit unaided (> usually achieved at 6–8 months). He was able to pull himself up with support at 14 months. At 17 months he was able to stand with support (> usually achieved at approximately 8 months). When he last presented at the age of 22 months the patient had started to take his first steps around the furniture (> usually achieved at 8.5–12 months) and was able to move forwards and backwards in a ride-on car. His grip and fine motor skills developed at an age-appropriate rate. The effect of the treatment on early motor development in the patient were reflected in the total CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Development) score (▶ **Fig. 2**). To date, the patient has no signs of onset of scoliosis or contractures. As part of the multidisciplinary and multimodal therapy management demanded by SMA, the patient had age-appropriate supportive equipment such as orthotics, standing frames, a therapy chair and rehab stroller.

Evaluation

The example of the infant with type 1 SMA confirms the need for a diagnosis to be made as early as possible and immediate initiation of treatment. While his sister who also had SMA died at the age of only 8 months, thanks to the prenatal diagnosis and treatment with nusinersen from the age of 2 weeks, significant success was achieved. The patient's physical development is almost age-appropriate. He did not require ventilation and checked off motor development milestones that would not have been expected in a patient with manifest type 1 SMA. The intrathecally administered antisense oligonucleotide authorized mid-2017 is the first drug specifically licensed to treat 5q-SMA that counteracts the progressive degeneration of the motor neurons [2]. The experience in this case confirms the current interim results of the NURTURE study that is exploring the benefits of early diagnosis and presymptomatic start of therapy with nusinersen in infants (n = 25) with genetically confirmed type 1 5q-SMA [3]. After a median observation period of 33.9 months, all 25 children were still alive and none needed permanent ventilation. They had reached the motor development milestones and their development was age-appropriate [3]. Given the multifaceted nature and severity of the symptoms and comorbidities, a multi-modal treatment approach and multidisciplinary disease management are required. For this reason, those affected should be referred to a specialist center at an early stage (http://bit.ly/SMA-DGM).

Authors



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Case 3

Three-year-old female patient with 5q-SMA recovers motor function under treatment with nusinersen

SUMMARY

The patient was diagnosed with 5q spinal muscular atrophy (5q-SMA) at roughly 2 years of age. At this point her motor function was already severely affected and she was not able to sit or stand, let alone walk unaided. Treatment with nusinersen (Spinraza®) was introduced at the age of 3 years.

Only 6 months after the treatment was initiated, the first significant improvements in her motor function were already evident. The patient recovered motor development milestones that she had achieved briefly in early childhood but that she had gone on to lose as the disease progressed unhindered by causal treatment.

Click here for patient videos
Link: https://eref.thieme.de/ESIRV

Medical history

The now 3-year-old patient (height 95 cm, weight 11 kg) presented at the age of 2 years. The parents reported that the girl had not demonstrated any abnormalities over the course of the year. They said that as a baby she tended to be quiet and not particularly mobile. She started crawling at 12 months but had never been able to stand up on her own and remain standing without support. She was also unable to sit down unaided. In the subsequent months she then also lost the ability to crawl.

Diagnosis and current findings

The first genetic test was carried out in July 2017. The patient was diagnosed with homozygous deletion of exons 7 and 8 in the SMN1 gene on chromosome 5 with 3 copies of the SMN2 gene. Thus, the genetic test confirmed the suspected diagnosis of 5q spinal muscular atrophy. SMA is a rare, autosomal, recessive hereditary neuromuscular disease resulting in progressive proximal muscle weakness and atrophy, often affecting the leg muscles in particular [2]. The mutations on the SMN1 gene mean that patients with SMA produce too little survival-motor-neuron (SMN) protein, resulting in the death of the second motor neuron in the bone marrow. Untreated children will hardly ever reach new motor development milestones if they have a particularly severe form of SMA. Once the disease has manifested, progressive muscle weakness leads to a loss of motor function, and if left to run its natural course, lost motor functions will never be recovered. In the physical and neurological examination carried out when the diagnosis was made, just before the start of treatment, the 3-year-old girl was unable to sit down from a standing position unaided. She was only able to sit independently if placed in that position. She was only able to move around with a strenuous commando crawl. When placed in a supine position she was not able to actively raise her legs against the force of gravity. In a prone position she was only able to raise herself up on her lower arms but not on her hands (▶ **Fig. 1**). On the motor function scale HFMS (Hammersmith Functional Motor Scale) for patients with spinal muscular atrophy her peak score was 28 out of a maximum of 40 points before treatment was initiated in July 2018. There was still a slight delay in her language development, coming from a bilingual environment. The patient had special educational therapy and physiotherapy.

▶ **Fig. 1** Before starting treatment the patient (3) was only able to commando crawl. The complete video is available in the Thieme Infothek (German): QR code at the start of the article.

▶ **Fig. 2** 6 months after the start of nusinersen treatment (3) the patient is able to stand independently for a short time and walk a few steps with support. The complete video is available in the Thieme Infothek (German): QR code at the start of the article.

Therapy and disease progression

In July 2018, directly after the diagnosis of 5q-SMA, the patient was started on a treatment with nusinersen at the age of 3 years and 3 months. The substance was administered intrathecally by lumbar puncture into the cerebrospinal space of the spinal canal at doses of 12 mg/5 ml in accordance with the summary of product characteristics [3]. In the initial loading phase the injections were given on days 0, 14, 28 and 63. Since the last loading dose on day 63 she has been given a maintenance dose (12 mg/5 ml) at intervals of 4 months. So far there have been no complications in the lumbar puncture or intrathecal administration of the active substance. The girl tolerates the treatment very well and has had no undesirable effects or post-puncture complaints. Six months after starting treatment with nusinersen, she was again able to crawl. This therapy outcome is all the more notable, as she had already learned to crawl at the age of 12 months but then lost this ability due to progressive muscle weakness. She is also able for the first time to sit unaided and to pull herself up to a standing position without assistance. She can stand on her own for a short time. With the support of somebody holding her hands she is now even able to walk a few steps (▶ **Fig. 2**). She can sit unaided for long periods and does not tire. Within 6 months, her HFMS score improved from 28 points (July 2018) to 35 points (January 2019).

Assessment of the therapy and the case study

The case study of the 3-year-old patient confirms the good efficacy and tolerance profile of nusinersen in the treatment of 5q-SMA. Before SMA manifested she had learned to crawl but then lost this skill as the disease progressed. She did not reach the majority of the age-appropriate motor development milestones prior to starting treatment. Under treatment with nusinersen within the first 6 months she learned to sit down independently, crawl and pull herself into a standing position. She has taken her first steps with assistance. The motor function advances that would never have occurred without nusinersen treatment are also reflected in the higher score in the HFMS motor function tests, with an improvement from 28 to 35 points. The lumbar punctures were carried out without complications and there were no undesirable effects. The nusinersen drug treatment is accompanied by special educational therapy and physiotherapy. This case also shows how important it is to immediately carry out a genetic test as soon as 5q-SMA is suspected, and to initiate the causally effective antisense oligonucleotide treatment as early as possible before motor functions are irreversibly lost.

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Case 4

15-year-old male patient with type 3 SMA and late diagnosis – Transition from pediatrics to neurology

SUMMARY

A 15-year-old patient was diagnosed with type 3 5q spinal muscular atrophy (5q-SMA) at the age of 13 years. Proximal muscle weakness newly perceived at puberty, affecting the legs in particular, with a deterioration of gait and positive Trendelenburg sign, were key for the diagnosis. Treatment with the antisense oligonucleotide nusinersen (Spinraza®) counteracted further loss of motor function and even resulted in functional improvement.

Click here for patient videos
Link: https://eref.thieme.de/VE9F6

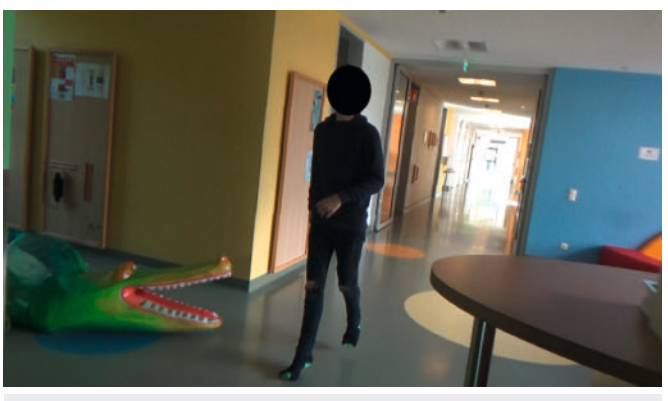
Medical history

The now 15-year-old patient (height 168 cm, weight 55.3 kg) has always been described as a little clumsy. According to his parents he has never enjoyed sport. His gait has also always been somewhat remarkable, with a tendency to tiptoe. At the onset of puberty his motor skills deteriorated within the space of only a few months and in the neurological test the patient had a new, notable waddling gait with positive Trendelenburg sign. The boy was not able to hop or run properly with a flight phase. He could only stand up by supporting himself with his arms. When he stood up from a seated position with his legs outstretched, Gower's sign was notable. He also found it very difficult to climb the stairs, which he was only able to do slowly and with effort. In general, he tired quickly following any physical activity. The patellar reflex could not be elicited. The symptoms and findings suggested 5q spinal muscular atrophy, a rare neurodegenerative disease caused by the death of motor neurons in the bone marrow, which left untreated leads to progressive proximal muscle weakness and atrophy affecting the legs in particular [1, 2]. Once the disease has robbed the body of muscle strength and motor function, it is not expected that these functions can be restored. The disease is caused by a loss of function or a defect in the SMN1 gene (survival of motor neuron) on chromosome 5q [1, 2].

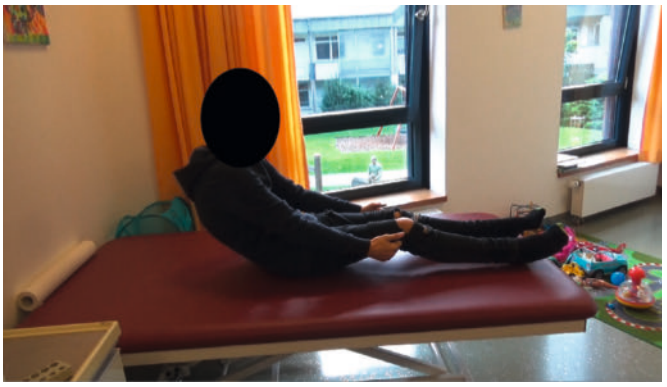
Diagnosis and therapy

A preliminary diagnosis of late onset SMA was confirmed by genetic testing in November 2016 with evidence of homozygous deletion of exons 7 and 8 in the SMN1 gene in 4 copies of the SMN2 gene on chromosome 5q (type 3 SMA). The patient was already 13.5 years old when diagnosed. In the Hammersmith Functional Motor Scale Expanded (HFMSE) for spinal muscular atrophy, he scored 61 out of 66 points before the start of drug treatment. In the 6-minute walk test he managed 550 meters (normal value for healthy individuals is approximately 700–800 meters).

The treatment with the antisense oligonucleotide nusinersen was started on 20 October 2017. The drug was administered intrathecally by lumbar puncture with 12 mg per individual dose every 4 months as per the summary of product characteristics [3]. At the start of the treatment he was given loading doses on days 0, 14, 28 and 63. Nusinersen was administered with no complications or post-puncture symptoms. There were no undesirable effects during treatment.



▶ **Fig. 1** Just 6 months after the start of therapy the patient's flight phase had lengthened again. The complete video is available in the Thieme Infothek (German): QR code at the start of the article.



▶ **Fig. 2** 12 months after the start of nusinersen treatment, the patient was able to stand up from a seated position with his legs outstretched without any additional support. The complete video is available in the Thieme Infothek (German): QR code at the start of the article.

Further disease progression

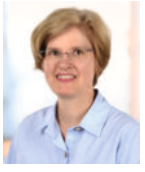
After the patient had exhibited a continuous and considerable deterioration in his motor function over the course of about 2 years due to the SMA, just 6 months after starting nusinersen treatment a significant improvement in his mobility was observed. He found it easier to climb stairs. His endurance in physical activities had also notably increased even at this early point in time. He was able to run again with a flight phase (▶ **Fig. 1**). The progress in his motor function also continued over the longer term. Twelve months after the start of treatment he was able to climb 3 flights of stairs without taking a break. He could run without tripping and continued to experience the flight phase. He could stand up much quicker from a seated position with his legs outstretched and did not have to support himself with his arms (▶ **Fig. 2**). He was once again able to hop on the spot.

The patient has been treated with nusinersen for 1 year and 8 months now. In March 2019 he scored 63/66 in the HFMSE. At the last examination on 27 June 2019, he managed a distance of 670.5 meters in the 6-minute walk test, an improvement of 120.5 meters compared to the value before the start of treatment, and already very close to the normal healthy range (700–800 meters). Until he reaches adulthood he will continue to be treated at the Pediatric Hospital of the Ruhr University Bochum. It is then planned that colleagues at the Neurology Department of the Ruhr Valley Neuromuscular Center (Muskelzentrum Ruhrgebiet) will take over his treatment. The referral is with direct contact and transfer of all relevant information, and ensures that interdisciplinary care is continued.

Assessment of the therapy and the case study

This case of a 15-year-old male patient with genetically confirmed 5q-SMA with late disease onset (type 3 SMA) illustrates that distinctive improvements in motor function and muscle strength and endurance that patients can perceive themselves can be achieved with the reversible splice modulator nusinersen even if the patient is not diagnosed until adolescence. The patient benefited considerably from specific effective drug treatment, even in the first 6 months after the start of therapy, in terms of mobility on a flat surface and climbing stairs. Nusinersen not only counteracted further loss of motor functions but even resulted in functional improvements. After 12 months of treatment, further advances were evident in his speed and movements when running, standing up and climbing stairs. He was once again able to hop on the spot. The improvement in motor function was associated with good tolerance of nusinersen. To date, no undesirable effects of the treatment have been observed.

Authors



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Case 5

Subjective improvement in respiratory insufficiency in an adult patient with advanced type 2 SMA under nusinersen

SUMMARY

5q spinal muscular atrophy (5q-SMA) can affect not only the skeletal, but also the respiratory muscles and necessitate ventilation. The case of a 34-year-old male patient badly affected with type 2 SMA shows that intrathecal treatment with nusinersen (Spinraza®) is an option despite pronounced scoliosis and von Willebrand syndrome, and is associated with a subjective improvement in respiratory function.

Medical history

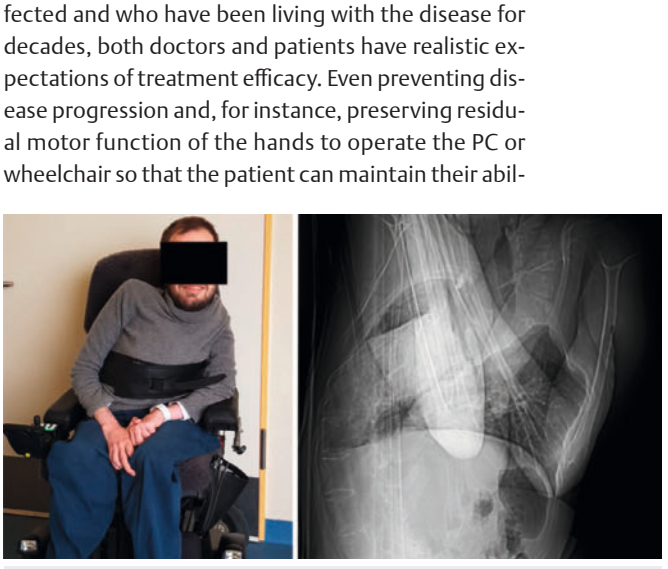
The 34-year-old man (height 166 cm, weight 50 kg) developed SMA in early childhood. The first symptoms appeared when he was 18 months old and type 2 SMA was diagnosed by muscle biopsy when he was 2 years old. As a young child he had difficulty standing independently. He never achieved the motor development milestone of walking independently. While he did learn to sit unaided and crawl, he had lost these functions again by the age of 10 years. The patient has been fully dependent on the use of a wheelchair since the age of 4. As the disease progressed, the function of his respiratory muscles also deteriorated. Since the age of 20 the patient has required non-invasive ventilation for up to 16 hours a day. His vital capacity is 0.9 l, equivalent to 20 % of target. He can have oral nutrition, and so to date he has not needed tube feeding. As well as joint contractures, he has also developed pronounced scoliosis (▶ **Fig. 1**) which required stabilization of his spine in July 2001. As the patient also had von-Willebrand syndrome the surgery had to be canceled due to bleeding complications.

Diagnosis and therapy

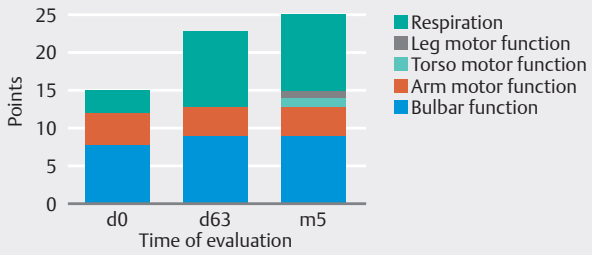
Before the licensing of nusinersen for the treatment of 5q-SMA [1], the disease was treated according to the standards applicable at the time [2]. The multimodal therapy concept included ongoing outpatient physiotherapy and ergotherapy as well as inpatient rehabilitation to ensure the best possible preservation of muscle function and to avoid secondary complications. The patient was also given assistive equipment, his nutrition, lung function and respiration were monitored and he underwent orthopedic therapy for scoliosis and contracture. In August 2018, SMA caused by homozygous deletion of exons 7 and 8 in the SMN1 gene on chromosome 5 was genetically confirmed. Three copies of the SMN2 gene were also verified. Drug treatment with nusinersen, an antisense oligonucleotide to modify the splicing process, was initiated in February 2019. According to the summary of product characteristics [1] the substance is administered intrathecally at a dosage of 12 mg by lumbar puncture. For a 2-month period, 4 loading doses (days 0, 14, 28 and 63) were administered and the patient then receives a maintenance dose of 12 mg nusinersen every 4 months.

Disease progression

Although the observation period is certainly still too short to be able to assess a lasting efficacy, the first effects of nusinersen treatment are already evident. In the treatment of adult patients who are severely affected and who have been living with the disease for decades, both doctors and patients have realistic expectations of treatment efficacy. Even preventing disease progression and, for instance, preserving residual motor function of the hands to operate the PC or wheelchair so that the patient can maintain their abil-



▶ **Fig. 1** 34-year-old patient with advanced spinal muscular atrophy type 2 with significant scoliosis [Source: Dr. O. Schreiber-Katz and Dr. A. Osmanovic].



▶ **Fig. 2** Self-assessment of functional disability in activities of daily living. (ALSFRS-R/12 Items; items 1–3 bulbar function, items 4–6 arm motor function, item 7 torso motor function, items 8–9 leg motor function, items 10–12 respiration; 0–48 points).

ity to work and their day-to-day independence, is a considerable benefit. In this patient, after 2 months (4th dose of nusinersen) changes in various parameters can be observed compared to baseline: His score in the ALSFRS-R (revised Amyotrophic Lateral Sclerosis Functional Rating Scale) improved from 15 out of 48 at baseline to 25 with a significant reduction in subjective dyspnea or orthopnea and an improvement in respiratory function (▶ **Fig. 2**). At the same time his RULM (Revised Upper Limb Module) score increased from 10 to 13 points (out of 37 points). There were also significant improvements in his perception of his current general state of health according to the quality of life questionnaire EQ-5D-5L™. On the visual analogue scale (0–100 points) of the questionnaire an increase from 50 to 80 points was recorded. His quantifiable scores relating to motor function also slightly improved. The sum score in the MMT (Manual Muscle Testing) (0–10) rose from 309 at baseline to 347 points after 2 months. In the HHD (Hand Held Dynamometry) the patient's score improved for elbow flexion on the right and foot lift bilaterally. In this early phase of treatment there is even an improvement and not merely stabilization in the subjective and quantifiable outcome parameters.

The Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) used in the marketing authorization studies as a motor function test in children lacks the sensitivity required to record changes that primarily involve gross motor function of the legs and torso, especially in adult patients with tetraparesis (type 2). We therefore also use the RULM score and other quantifiable, objective and subjective parameters so that we can also record smaller therapeutic effects.

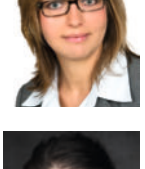
CONCLUSIONS FOR CLINICAL PRACTICE

The experience we have with type 2 SMA patients has thus far confirmed the feasibility and good tolerability profile of nusinersen treatment. The therapy requires an experienced, interdisciplinary treatment setting. Potential therapeutic effects aside from motor function should be evaluated over the long term by suitable parameters such as Patient Reported Outcomes (PRO) in these severely affected patients.

Evaluation

As the patient had scoliosis, the intrathecal administration of nusinersen was performed under CT guidance in an inpatient setting. Since the patient had von-Willebrand syndrome, a primary prophylactic administration of coagulation factor VIII/vWF preparations was required at a dose of 30–50 I.U./kg body weight. Under this treatment it has thus far been possible to administer nusinersen safely and without bleeding complications. Aside from mild headache after the 4th intrathecal dose, the patent tolerated the treatment with nusinersen well. In summary, the case of the 34-year-old man with type 2 SMA shows that nusinersen can also be used safely in adults at a progressive stage of the disease and with significant scoliosis – even in cases with hemorrhagic diathesis. The CT-guided lumbar puncture in an experienced, interdisciplinary setting has proved to be a safe application method. Puncture-associated undesirable effects were reported but there were no serious undesirable effects. Subjective parameters show an improvement in respiratory function. Slight trends that indicate a positive therapeutic effect can be seen in the early course of treatment and in further outcomes.

Authors



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Case 6

Improvement in long-standing type 3 5q-SMA with nusinersen treatment

SUMMARY

5q spinal muscular atrophy (5q-SMA) can emerge at any age with varying degrees of severity. Type 3 SMA usually manifests after the age of 18 months. However, symptoms may not appear until puberty. The following case shows that even adults diagnosed with SMA in their youth and with progressive muscle weakness and atrophy can benefit from treatment with nusinersen.

Medical history

The now 22-year-old patient noticed the first signs of muscle weakness at the age of 13 to 14 years when his physical performance in sports such as athletics, cycling and especially running declined. A technical product designer, he then gradually developed progressive weakness in his legs, primarily in the proximal region, with atrophy of the upper leg muscles which later went on to affect the lower leg muscles. Since then he has also had progressive, almost continuous pain, mainly in both upper legs. The pain was so intense that he had to take regular analgesia. He was initially prescribed pregabalin and then later tapentadol, which he continues to take and which keeps him pain-free most of the time. Following respiratory infections in the past he had several episodes of transient, self-limiting but significant worsening of the muscle weakness which manifested as severe, proximal tetraparesis. Within days to weeks, the paresis then returned to baseline. A few months before he presented at our hospital the patient and his mother both noticed that the muscle weakness was no longer just limited to the lower extremities. His arm and shoulder girdle muscles were now affected by a slowly progressing weakness and atrophy that was more pronounced in the proximal region. In his daily life, this was especially evident in difficulties in over-the-head movements, such as drying his hair with a hairdryer.

The family history was unremarkable. In neither the parents, grandparents or step siblings on the mother or father's side of the family were similar symptoms observed. An aunt on his father's side has multiple sclerosis.

Diagnosis and current findings

When he was 15, a molecular genetic test was performed showing homozygous deletion of the exon 7 and 8 of the SMN1 gene on chromosome 5 and 4 copies of the SMN2 gene and thus the tentative clinical diagnosis of 5q-SMA type 3 (juvenile SMA, Kugelberg-Welander) was confirmed. Both the patient's parents and his grandmother on his mother's side of the family were found to be carriers in the molecular genetic test, with the heterozygous form of the aforementioned mutation.

In the current neurological examination of the now 22-year-old patient, proximal atrophic tetraparesis was observed which was more pronounced in the legs, with significant atrophy of the upper legs, and less pronounced atrophy of the muscles in the lower legs and the upper arms and shoulder girdle. The paresis was most pronounced in the knee extension (bilateral muscle strength 1–2/5) and hip flexion (right 3+/5, left 3-/5). Fasciculations of the upper legs were also observed. These were also evident, but less pronounced in the upper arm and shoulder girdle muscles. He was able to do one squat using compensation strategies. The patient was not able to raise his legs from a supine position. He could walk 728 meters in the 6-minute walk test, and could walk without stopping for about 1 kilometer. For very long distances he sometimes had to resort to using a wheelchair. In the motor function scores developed especially for patients with SMA and regularly used in clinical studies, the patient scored full marks in both the function of torso and leg muscles (Hammersmith Functional Motor Scale Expanded, HFMSE) and in the arm and shoulder girdle muscles (Revised Upper Limb Module, RULM) (HFMSE: 66/66 points, RULM: 37/37 points).

Treatment and disease progression

When he was 21, intrathecal nusinersen treatment administered by lumbar puncture was initiated. In accordance with the summary of product characteristics [1] the patient was first given 4 loading doses on days 0, 14, 28 and 63. He then switched to intrathecal

▶ **Tab. 1** Scale of muscle strength according to the Medical Research Council (MRC) before starting nusinersen therapy and after 6 months.

	before the start of treatment		six months after the start of treatment	
	right	left	right	left
Hip extension	2–3/5	4–5/5	5/5	5/5
Hip flexion	3+/5	3–/5	5–/5	4+/5
Knee extension	1–2/5	1–2/5	4/5	4/5
Knee flexion	5–/5	3–4/5	5–/5	5–/5
Arm abduction	4+/5	4+/5	5/5	5/5

administration every 4 months. After just 28 days he noticed an improvement in the strength in his legs and reported that his mobility overall had improved. In line with his subjective perception, the neurological examination showed a slight improvement in the strength in his legs, especially in the knee extension.

After 63 days the patient reported further improvement in his strength, especially in his legs. He was even able to do a series of squats and to raise his legs when in a supine position and hold them raised for a short time. Six months after starting treatment with nusinersen he reported that the muscle strength in his legs had improved further still. In his day-to-day life, he can now walk longer distances without the need for a wheelchair. He also finds walking up stairs easier. He also reports that he feels he has more endurance in various motor activities in his daily life. In the neurological examination at this point a significant improvement in the strength of his lower extremities could be measured (▶ **Tab. 1**). In the specified motor function score he continued to gain full marks. His 6-minute walk test score remains virtually unchanged at 718 meters. He continues to feel the positive effect of nusinersen treatment even after 18 months.

To date, the patient has tolerated the treatment well in general. There were also no serious complications from intrathecal administration by lumbar puncture.

The only undesirable effect observed in this patient after the lumbar puncture was what is known as postdural puncture headache, where he suffered headache and backache which persisted after some treatments for up to 2 weeks. This is a generally known side effect of a lumbar puncture.

Assessment of the therapy and the case study

In this adult patient with type 3 SMA, treatment with nusinersen resulted in a significant improvement in strength, especially in the lower extremities, in only a short period of time. As the patient already scored full marks in the SMA-specific motor function scores (HFMSE and RULM) before treatment started, this improvement could not be objectified in these scores, but was shown clearly in the MRC strength tests, which are also often used to observe progression in SMA patients.

The positive effect of the treatment with improvements relevant to daily life is still continuing after 22 months of ongoing treatment. The adaptation of existing, or the development of new SMA-specific motor function scores, particularly for adult patients with very poor or comparatively good motor function baseline, would be beneficial so that the progression of the disease under treatment can be better and more accurately documented.

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Case 7

Nusinersen in the treatment of type 2 SMA with complex spinal anatomy

SUMMARY

5q spinal muscular atrophy (5q-SMA) can lead to severe scoliosis in advanced stages, requiring surgical spinal alignment with metal implants. This can make intrathecal administration of nusinersen more difficult. Alternative approaches for intrathecal administration by lumbar puncture may be required. The case of a 25-year-old female patient with type 2 SMA and complex spinal deformities shows how the antisense oligonucleotide can be administered via alternative routes with neuroradiological guidance.

Medical history

This 25-year-old patient displayed the first motor function deficits when she was 1 year old. A molecular genetic analysis showed homozygous SMN1 deletion of 3 copies of the SMN2 gene which led to a diagnosis of type 2 SMA. She was able to sit up on her own up to the age of 12 years. She was never able to walk unaided. She developed scoliosis at an early stage and at the age of 4 underwent surgery with expandable rods. Treatment outcome was discussed with the patient and stabilizing disease progression with preservation of the residual motor function in her fingers was defined as a realistic treatment objective, as she considered the ability to write very important for her job.

Current findings and therapy planning

The clinical neurological examination showed hypotonic, severe tetraparesis with paralysis of the legs and proximal arms, but she still had a strength rating of 2 to 3 for flexion and extension of her hands and fingers. The motor function score before the start of treatment was 0 points on the Hammersmith Functional Motor Scale Expanded (HFMSE), 2 points on the Revised Upper Limb Module (RULM) and 28 points on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). The lung function examination showed reduced vital capacity of 650 ml. After the first CT images were taken it was evident that there could be no conventional interlaminar approach for the patient due to complete lumbar fusion and the absence of a bone window (▶ **Fig. 1A**). In the literature, transforaminal [2, 3] and cervical puncture [4, 5] are discussed as alternative approaches. Subcutaneous intrathecal catheter systems have also been used to administer nusinersen into the cerebrospinal fluid space where an approach is problematic [6].

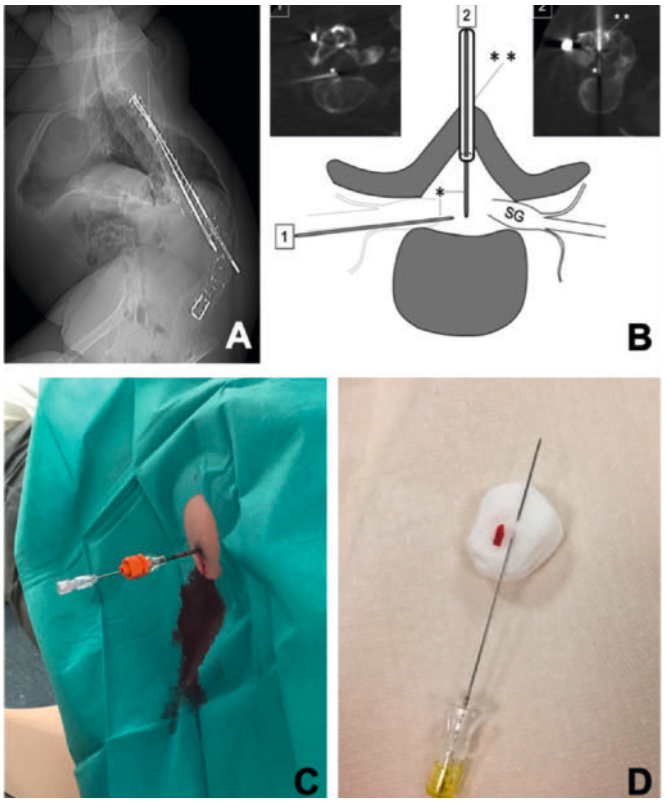
Transforaminal access

In contrast to a dorsal lumbar puncture between the spinous processes, a transforaminal puncture of the lumbar cerebrospinal fluid space was considered as an alternative. After the intervention and the possible risks involved were explained to her, the patient gave her consent. There were no complications during puncture of the L4 root (▶ **Fig. 1B**) and so the transforaminal approach was also selected for subsequent injections. After the 2nd treatment the patient complained of lumbar pain syndrome and postdural puncture headache, requiring hospitalization. Clinical neurological tests and laboratory results were normal. Imaging also showed no sign of spinal bleeding. After sufficient analgesic therapy the symptoms quickly receded and the patient could be discharged the following day.

Translaminar approach

Before the 3rd treatment the option of keyhole laminotomy and the risks (▶ **Fig. 1B**) were discussed with the patient as an alternative to transforaminal puncture. Risks include injury of the dura with the potential threat of severe loss of cerebrospinal fluid, injuries to the blood vessels or nerve structures and an increased risk of infection. However, a potential benefit is the option of a permanent osseous access. After the procedure was explained to the patient she consented to the translaminar therapy. To prevent peri-interventional pain, 5 ml mepivacaine 2 % was infiltrated deep close to the periosteum.

Sedation was not necessary. The hole was drilled at L 3/4. The diameter of the needle for the bone biopsy was 11 G (3 mm) with a length of 102 mm (▶ **Fig. 1C**). The dura was punctured with a conventional 20 G spinal needle (▶ **Fig. 1D**). There were no complications during the drilling procedure, and what is especially important is that the patient did not feel any relevant



▶ **Fig. 1** Illustration of transforaminal and translaminar approaches for intrathecal administration of nusinersen in a 25-year-old female patient with type 2 SMA. **(A)** CT topography showing the entire spine. A complex spinal anatomy with metal implants is evident. **(B)** Diagram illustrating the approaches used. The first 2 treatments were administered by transforaminal puncture (1) with a 20 G spinal needle due to complete fusion of the lumbar spine. For anatomical reasons, the neuroforamen in the anterior region had to be punctured. In subsequent treatments a translaminar keyhole approach (2) at L 3/4 was used. A spinal needle was inserted into the spinal canal coaxially to the biopsy needle. **(C)** Peri-interventional positioning of the 11 G biopsy needle with coaxially inserted spinal needle **(D)** 20 G spinal needle next to the collected bone cylinder measuring 3 mm.

CONCLUSIONS FOR CLINICAL PRACTICE

The case report shows that intrathecal treatment with nusinersen can also be given to adult SMA patients with significant scoliosis and spinal metal implants. Successful and safe treatment of these patients demands the support of imaging procedures and experienced neuroradiologists. Radiation exposure involved in repeat treatments of young patients should be taken into account. The translaminar keyhole method expands the range of potential approaches.

pain. The bony channel could be used again for the 4th and 5th injection. It is designed to provide a permanent approach for maintenance therapy, however the risk of closure due to ossification over the longer term cannot be ruled out. The average intervention time, measured from completion of the topogram through to administration of the drug was 10.5 min for the transforaminal puncture and 11 min for the subsequent translaminar injections.

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Case 8

Treatment with nusinersen can improve daily life – even in older age patients with SMA

SUMMARY

The patient presented here noticed the first signs of muscle weakness in early childhood. The now 54-year-old patient has had musculoskeletal pain and gradually progressive muscle weakness in her legs all her life, until the age of around 50, when she lost her ability to stand and walk. She was diagnosed with type 3 5q spinal muscular atrophy (5q-SMA) at the age of 32. Although she did not start treatment with nusinersen (Spinraza®) until the age of 54, it resulted in a significant improvement in her motor function.

Medical history

Looking back, this patient developed the first symptoms of SMA at the age of 1–2. She was walking by 14 months, but her leg weakness manifested as "knock knees" (genu valgum), difficulties standing up and Gower's sign, using her hands to "climb up" her legs. From the age of about 5 she was walking and running much more slowly than children of the same age. She was only able to walk about 50 m. She also found it difficult to climb trees and carry heavy objects. Over the years and decades that followed she gradually lost more and more strength in her legs. Even in childhood she had to use a wheelchair for long distances. After a metatarsal fracture at the age of 32 the strength in her legs declined again rapidly. By the time she reached about 40 she could only walk about 40 m at a stretch using a walking stick, and by 50 her legs then "suddenly" failed altogether. Since this point she has not been able to stand and has been fully dependent on a wheelchair. She had to give up driving because she was no longer able to get in and out of the car. At the same time the strength in her arms and hands also progressively declined, with the left side affected more significantly than the right. Since she was young her hands have always shaken whenever she holds anything. She often has twitching of the muscles, including the thigh and calf muscles. She has had breathing difficulties since she was a child which manifested as dyspnea on exertion. This has become more pronounced over the years.

Since the age of 30 she has had severe, generalized musculoskeletal pain, especially in her back, neck and calf muscles, which is why she used to take flupirtine on demand (until the marketing authorization was withdrawn).

She regularly does physiotherapy exercises twice a week alternating with manual therapy. An attempt to treat the patient with intramuscular injection of growth hormones at the age of 36 did not bring about any improvements.

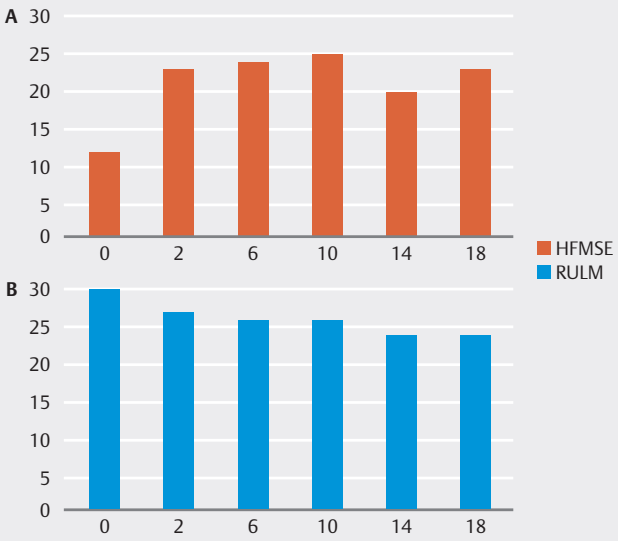
Diagnosis and current findings

During childhood and in early adulthood no clear diagnosis could be made, despite a muscle biopsy at the age of 3 and multiple hospitalizations in pediatric and neurological hospitals. Limb-girdle muscular dystrophy was suspected. Finally at the age of 32, a diagnosis of SMA was confirmed by molecular genetic testing. At the age of 43 a supplementary molecular genetic test confirmed homozygous deletion of exons 7 and 8 of the SMN1 gene. The number of SMN2 gene copies was not determined. In molecular genetic tests both parents had a heterozygous deletion of exons 7 and 8 of the SMN1 gene.

Before the start of treatment with nusinersen, the patient scored 11/66 in the Hammersmith Functional Motor Scale Expanded (HFMSE) and 29/37 in the Revised Upper Limb Module (RULM) scale. She was not able to stand or walk independently.

Treatment and disease progression

At the age of 53 intrathecal treatment with nusinersen was initiated and administered by lumbar puncture with loading doses on days 0, 14, 28 and 63, followed by maintenance treatment at intervals of 4 months in accordance with the summary of product characteristics [1]. After roughly 2 months the patient noticed a significant improvement in strength and endurance. Her HFMSE score doubled from baseline to 22 out of 66 points. At this time there was a measurable improvement in her motor function relevant to her daily life, which has persisted to date. Since then she is again able to stand unaided for a few seconds, which has a



▶ **Fig. 1** Development of the motor function scores HFMSE **(A)** and RULM **(B)** before (0) and during treatment with nusinersen (in months).

CONCLUSIONS FOR CLINICAL PRACTICE

The case of this patient shows that a significant improvement in motor function relevant to daily living can be achieved with nusinersen even in older adult patients. The extent of the improvement of motor function does not appear to correlate either with age or with the type of SMA, but with the extent and timescale of the motor function limitations before the start of therapy, as experience of other adult patients with SMA has shown. Patients who notice a significant deterioration in motor function just before the start of treatment but in whom a relatively large number of motor functions are preserved and whose muscle atrophy is less pronounced appear in particular to benefit from the treatment.

particularly beneficial effect in getting in and out of the wheelchair. In the RULM score, however, there was a slight drop by 3 points which did not correlate with the patient history. About 5 months after the start of nusinersen treatment, during rehabilitation treatment, the patient also noticed that the pre-existing pain was more intense, especially in the neck and shoulder girdle muscles, and to a lesser extent in the lumbar region. The fact that the pain became more intense after an inpatient rehabilitation treatment with intensive physiotherapy indicates that the muscles were strained by the physiotherapy and that this is at least partially responsible.

In terms of motor function, a further slight improvement in the HFMSE score was observed over the course of treatment (▶ **Fig. 1A**). In parallel, however, the RULM score fell by 6 points to 23 points (▶ **Fig. 1B**). This is probably due to the musculoskeletal pain which affected performance of the items in the motor function score, especially in the RULM score. After 18 months of treatment with nusinersen, the pain spontaneously improved along with her HFMSE score, rising from 19 to 22 points. Before this her HFMSE had also seen a short-term drop. Despite the fluctuations in the motor function score, the patient reported subjectively that she had a consistent and significant improvement in motor function under treatment with nusinersen with a positive effect on day-to-day life.

Assessment of the therapy and the case study

Nusinersen treatment resulted in a significant improvement in the patient's motor functions after only 2 months and a recovery of motor development milestones. Since then she has been able to stand unaided for a short time. There was no clear explanation for the occasional increase in pre-existing musculoskeletal pain. An MRI of her head, cervical, thoracic and lumbar spine showed largely age-appropriate findings. It is suspected that her muscles were strained by rehabilitation therapy.

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