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ORIGINAL COMMUNICATION

Intrathecal administration of nusinersen in adolescent and adult SMA type 2 and 3 patients

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Abstract

Spinal muscular atrophy is a genetic motor neuron disease that leads to progressive muscular atrophy and muscle weakness. In December 2016, the Food and Drug Administration, and in June 2017, the European Medicines Agency approved the antisense oligonucleotide nusinersen for treatment of spinal muscular atrophy. Nusinersen has to be repeatedly administered intrathecally. Due to the clinical features of SMA, the application of the ASO by lumbar puncture can be challenging in symptomatic patients considering the frequently observed scoliosis, previous spine fusion surgeries, joint contractures, and respiratory insufficiency. To evaluate safety and feasibility of the intrathecal treatment in adolescent and adult SMA type 2 and 3 patients, we analyzed 93 lumbar punctures, monitored number of lumbar puncture attempts, duration of the procedure, injection site, and needle length. Oxygen saturation during the intervention, medication for sedation and local anesthesia, adverse events related to lumbar punctures, and macroscopic analysis of CSF were recorded. Moreover, we analyzed the use of CT-scans for performing lumbar punctures and its associated radiation exposure. Performing lumbar puncture for the intrathecal administration of nusinersen in adolescent and adult patients with later-onset SMA is feasible and safe, even in patients with complex spinal anatomies and respiratory insufficiency. To guarantee the quality of the procedure, we recommend establishing an experienced interdisciplinary team consisting of neurologists and/or neuropediatricians, anesthesiologists, orthopedic surgeons, and/or neuroradiologists.

Keywords Spinal muscular atrophy · Nusinersen · Lumbar puncture

Introduction

Spinal muscular atrophy (SMA) is a genetic and autosomal recessive motor neuron disorder clinically characterized by proximal spinal and bulbar muscle weakness and atrophy caused by degeneration of alpha motor neurons. With regard to the onset of clinical symptoms, the achievement of motor milestones, and life expectancy, SMA is divided into different subtypes (SMA type 0–4). Within the three main types (SMA type 1–3), SMA type 1 represents the infantile and thus the most severe form, while SMA types 2 and 3 are defined as late-onset forms and are characterized by intermediate (SMA type 2) or mild (SMA type 3) types of progression [1]. Pathogenetically, SMA is caused by a homozygous deletion in the SMN1 gene (survival motor neuron gene) on chromosome 5q13 [2]. So far, treatment of disease has been supportive, {e.g., physiotherapeutic measures, ventilation and secretion management, parenteral nutrition, and orthopedic treatment of scoliosis (see Guidelines of the Consensus Statement for Standard of Care in SMA 2007 [3])}. However, in December 2016 for the US and in June 2017 for Europe, the antisense oligonucleotide nusinersen has been approved for the treatment of SMA (see Guidelines of the Consensus Statement for Standard of Care 2018 [4, 5]). Nusinersen modulates the splicing process of the mRNA

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of the SMN2 gene, by inhibiting splicing factors and leading to increased integration of exon 7 into the mRNA, and thus increases the amount of SMN protein [6–8]. Clinical studies showed an improvement in motor function in children with infantile-onset SMA [9], late-onset SMA [10], and presymptomatic SMA [11]. Nusinersen cannot pass the blood–brain barrier and, therefore, has to be repeatedly administered intrathecally by lumbar puncture. An initial induction phase with the administration of 12 mg (5 ml) nusinersen on days 0, 14, 28, and 63 is followed by maintenance therapy at intervals of 4 months.

Due to the clinical features of SMA, the administration of the ASO by lumbar puncture can be challenging in symptomatic patients considering the frequently observed (roto) scoliosis, previous spine fusion surgeries, joint contractures on one hand, and the risk of deterioration of respiratory insufficiency particularly in case of a need for sedation on the other hand. Progressive scoliosis develops in SMA secondary to neuromuscular weakness [12] and often requires surgical intervention usually by growing rods [13] or definitive posterior spinal fusion to stabilize the collapsing spine [14, 15]. Respiratory insufficiency, reduced coughing, and mucus retention is typically observed early in SMA type 1 patients; in later-onset SMA patients, respiratory decline is often slowly progressive over the years, but progression varies between individuals [16].

In a previous single-center study with 20 SMA type 1 patients aged 2–50 months lumbar punctures for intrathecal administration of nusinersen could be performed without any relevant complications. Some of these treated patients had respiratory insufficiency, but no severe scoliosis was reported in this patient population [17]. Successful lumbar puncture with intrathecal administration of nusinersen was also possible in 28 children with SMA type 2 and 3 aged from 2 to 14 years, 13 of them with scoliosis, who were enrolled in a nusinersen clinical trial (phase I open-label study). Nearly half of the lumbar punctures were guided using fluoroscopy (44% of the attempted 74 lumbar punctures in 28 patients); only in one patient who had severe scoliosis the second fluoroscopically guided lumbar puncture procedure was not performed successfully [18]. Following studies showed that in SMA patients with severe scoliosis and/or extensive spinal hardware precluding standard posterior lumbar puncture fluoroscopy- or CT-guided lumbar transforaminal access made the injection of nusinersen possible [19–21]. In addition, cervical puncture technique was described for the administration of the drug in some children with SMA due to complex spine anatomies [22, 23]. These first data suggest that the administration of nusinersen in patients with SMA is possible even in patients with scoliosis and/or spine fusion operation and respiratory insufficiency, but larger studies need to confirm safety and feasibility of repeated intrathecal injections in SMA patients.

In this study, we report our single-center experience of repeated intrathecal administration of nusinersen in 20 adolescent and adult SMA type 2 and 3 patients aged 11–60 years, using 93 lumbar punctures.

Materials and methods

Patients

Adolescent and adult patients with SMA type 2 and 3 were treated with the antisense oligonucleotide nusinersen in the Department of Neurology at the University Hospital of Ulm during June 2017 to June 2018. Before we started treatment, patients were usually informed in detail during an appointment in our outpatient clinic about the results of pivotal studies [9–11] and also about insufficient evidence for drug efficacy in adolescent and adult patients so far. Only patients with genetically documented 5q-SMA were treated. Patients suffering from conditions, which could affect cerebrospinal fluid (CSF) circulation (e.g., history of other brain or spinal cord disease, shunt for CSF drainage, or central nervous system catheter), were excluded. Existence of spinal abnormalities [e.g., (roto)scoliosis and spine fusion operations] and respiratory insufficiency were no exclusion criteria to start therapy. Patients were further informed in detail about the lumbar puncture and the option of sedation for the procedure. In patients with spinal abnormalities, we informed about the potential need of imaging, more specifically, a CT-scan, to perform lumbar puncture for administration of the drug accompanied by radiation exposure. Most patients with aberrant spinal anatomies presented X-ray- and/or CT-images of their spine, which had been made in the past, for example, in perioperative situations. Preprocedural imaging was not carried out. In patients with respiratory insufficiency, we recommended an optimization of the respiratory situation with initiation or control of non-invasive ventilation if necessary before starting the procedure. We also made no restrictions regarding age and/or severity of disease, though SMA type 2 and 3 patients ≤ 16 years with no aberrant spine anatomies were treated by our colleagues in the Department of Pediatrics at the University hospital of Ulm. Severity of symptoms of disease was assessed prior to the first application (baseline) and after four injections of nusinersen (loading) by the Hammersmith Functional Rating Scale Expanded (HFMSE), a validated rating scale for SMA type 2 and 3 patients to monitor treatment success [24, 25]. The highest score to reach at Hammersmith is 66 points; lower values represent a more severe stage of disease. Mean HFMSE scores served for further analyses that were computed with paired Wilcoxon t test. Corresponding results were considered as statistically significant at a threshold of $p < 0.05$.

Lumbar puncture procedures

For the intrathecal injection of nusinersen, we used standardized protocols. Primary conventional lumbar punctures were intended in patients who did not present with severe scoliosis. In patients with a severe scoliosis and in patients with previous posterior spinal fusion operations where spine fusion material usually included the preferred lumbar puncture site, primary CT-guided lumbar punctures with the help of an orthopedic surgeon or neuroradiologist were planned.

Nusinersen was administered via lumbar puncture on days 1, 14, 28, and 63 in all patients and in some patients beyond on day 180 and 300. Dosage of nusinersen was 12 mg corresponding 5 ml. Lumbar punctures were in general performed with an atraumatic G22 needle (Sprotte). Needle length varied between 90 and 120 mm. In one patient [with the previous post-lumbar puncture syndrome (PLPS)], we tried once an atraumatic G24 needle (Sprotte); in another patient, we had to use an epidural needle G18 with Tuohy cut (for transforaminal injection). Needle position after lumbar puncture was confirmed by successfully drawing cerebrospinal fluid. After removal of 5 ml of cerebrospinal fluid (CSF), 12 mg nusinersen (5 ml) was administered intrathecally over 1–3 min.

Patients who were treated CT-guided were in a prone position all other patients were in a sitting or a lateral position for the procedure. Hip joint abnormalities required an individual positioning in the prone position on the CT table using blankets and pillows. In general, procedures were performed under the observation of an anesthesiologist. Patients dependent of intermittent ventilatory support used noninvasive ventilation (NIV) during the procedure. Patients received an intravenous needle to be prepared for emergency situations and for the use of intravenous drugs for an additional sedation or analgesia to be administered during the intervention. To prepare patients for the procedure, adolescents and some adults received a local anesthetic cream (e.g., lidocaine/prilocaine) on the injection site approximately 1 h before the intervention. Local anesthetic infiltration (e.g., mepivacaine) on the injection site was offered to the patients and used in long-lasting procedures by default. Premedication with the benzodiazepine lorazepam was offered to agitated and nervous patients before the procedure. If necessary, the benzodiazepine midazolam was administered intravenous before the intervention. In long-lasting procedures, we additionally gave low dose *S*-ketamine for sedation, because it induces only minor respiratory depression.

Interventions were carried out in our intervention rooms or the radiological facilities.

We monitored number of lumbar puncture attempts, duration of the procedure, injection site, and needle length. Oxygen saturation during the intervention, used medication for sedation and anesthesia, adverse events related to lumbar punctures, and macroscopic appearance of CSF were recorded. Moreover, we focused on the use of CT for performing lumbar punctures and the associated radiation exposure.

Results

Patients

Intrathecal injection of nusinersen was performed in 20 patients with SMA type 2 and 3 in the Department of Neurology at the University Hospital of Ulm since the approval of nusinersen in June 2017 until June 2018. Nine patients with SMA type 2 and 11 patients with SMA type 3 were treated, five of them ambulatory. Patients were aged 11–60 years (mean 32.80, SD 15.93). In detail, SMA type 2 patients were aged 11–48 years (mean 27, SD 16.12) and SMA type 3 patients were aged 13–60 years (mean 37.55, SD 14.80). Seven of the SMA type 2 patients had intermittent ventilatory support; four of them used NIV overnight (on average 8 h); three used NIV only when needed (in general less than 3 h in 24 h). Two of the SMA type 2 patients had a feeding tube [percutaneous endoscopic gastrostomy (PEG)]; in both cases, feeding tubes were placed in an emergency situation in the past and were currently not used for feeding. None of the SMA type 3 patients had ventilatory support or a feeding tube. All nine SMA type 2 patients presented with scoliosis; three had undergone previous spine fusion operation. Two of them had extensive posterior spinal fusion and one had growing rods; in none of these patients, lumbar region was spared of the graft material. A severe rotoscoliosis was present in six SMA type 2 patients. Two of the SMA type 3 patients had a scoliosis; one of them had an extensive posterior spinal fusion. Prior to treatment (baseline), the investigated patients revealed a mean HFMSE score (max. 66) of 17.3 (SD 23.26). Regarding the subgroups, mean HFMSE score was 1.67 (SD 2.18) in patients with SMA type 2 and 30.09 (SD 24.98) in patients with SMA type 3. After four applications of nusinersen, we observed a mean HFMSE score in all patients of 17.85 (SD 23.29) that did not differ significantly from baseline ($p = 0.148$). In addition, here, with a mean score of 2.00 (SD 2.45) in patients with SMA type 2, and a mean score of 30.82 (SD 24.80) in SMA type 3 after four injections of nusinersen, we found no significant differences in HFMSE scores from baseline within subgroups (SMA type 2: $p = 0.625$; SMA type 3: $p = 0.297$). Demographic and clinical data of all patients are summarized in Table 1.

Table 1 Demographics and clinical data of patients ($N=20$)

SMA	*N*	Age (SD; range)	HFMSE_0 (SD; range)	HFMSE_4 (SD; range)	NIV	PEG	Scoliosis	Spine operation
Total	20	32.80 (15.93; 11–60)	17.30 (23.26; 0–66)	17.85 (23.29; 0–66)	7/20 (35%)	2/20 (10%)	11/20 (55%)	4/20 (20%)
Type 2	9	27.00 (16.12; 11–48)	1.67 (2.18; 0–5)	2.00 (2.45; 0–6)	7/9 (78%)	2/9 (22%)	9/9 (100%)	3/9 (33%)
Type 3	11	37.55 (14.80; 13–60)	30.09 (24.98; 4–66)	30.82 (24.80; 4–66)	0/11 (0%)	0/11 (0%)	2/11 (18%)	1/11 (9%)

SMA spinal muscular atrophy, *N* number; *HFMSE_0* Hammersmith Functional Rating Scale Expanded at baseline (prior to first application of nusinersen), *HFMSE_4* Hammersmith Functional Rating Scale Expanded after four injections of nusinersen (loading), *NIV* non-invasive ventilation, *PEG* percutaneous endoscopic gastrostomy, *SD* standard deviation

Lumbar puncture procedures

In total, we performed 93 lumbar punctures for the injection of nusinersen in these patients. Every patient had at least four lumbar punctures according to the induction phase of the nusinersen treatment. Two patients had six, nine patients had five, and nine patients had four successfully performed lumbar punctures. In total, we performed 43 lumbar punctures in SMA type 2 (46%) and 50 lumbar punctures in SMA type 3 patients (54%). Lumbar punctures were carried out by a neurologist in case a conventional performed lumbar puncture was possible (39%). In case of a CT-guided lumbar puncture, the puncture itself was performed by an orthopedic surgeon (43%) or neuroradiologist (18%); drug application was always performed by a neurologist.

In total, 12 of the 20 patients (60%; mean age 28.83 years; SD 16.21) needed CT-guided lumbar puncture for the administration of nusinersen [57 of the 93 lumbar punctures (61%)]. In detail, we had to perform lumbar puncture CT-guided in all nine SMA type 2 patients who had either a rotoscoliosis or a previous spine fusion operation (100%) (Figs. 1; 2, 3, 4). In SMA type 3 patients, we had to use CT in three patients to perform lumbar puncture (14 lumbar punctures, 28%); the other eight SMA type 3 patients could be lumbar punctured conventionally without imaging support (36 lumbar punctures, 72%). One of the SMA type 3 patients treated with CT-guidance was a patient with scoliosis, in whom a first conventional lumbar puncture attempt was not possible. In a second SMA type 3 patient, CT-assisted lumbar puncture was necessary because of obesity (BMI 28) which made a conventional lumbar puncture impossible. In the third SMA type 3 patient, a primary CT-guided lumbar puncture was performed, because extensive posterior hardware precluded a conventional attempt.

In total, we needed 1.44 (SD 1.16) lumbar puncture attempts in all patients. When lumbar puncture was performed, CT-assisted 1.16 (SD 0.7) attempts were necessary; when conventionally performed 1.79 (SD 1.34), whereas this number includes the non-successful attempts in two SMA type 3 patients who were then treated CT-guided. In general, procedures lasted 20–150 min (mean 37.29 min, SD 17.69 min) from positioning of patients to successful administration of the drug; the mean duration of CT-guided lumbar puncture was 41.98 min (SD 19.88 min) and duration of the conventional lumbar puncture was 29.86 min (SD 9.89 min).

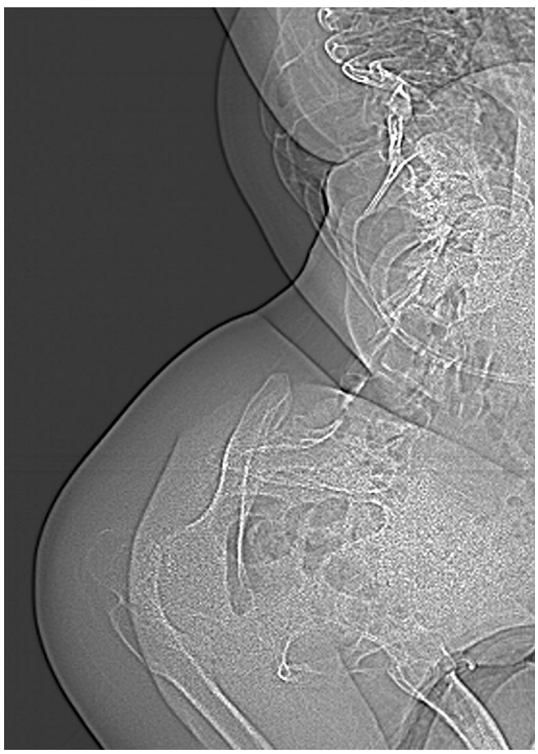

Fig. 1 CT-imaging shows the lower spine and pelvic region of a 45-year-old man with type 2 spinal muscular atrophy before intrathecal administration of nusinersen. Musculoskeletal changes with severe rotoscoliosic deformity and hip joint dislocation are demonstrated

Needle insertion site was L3/4 in 51% (47 lumbar punctures), L4/5 in 25% (23 lumbar punctures), L2/3 in 18% (17 lumbar punctures), and L5/S1 in 6% (6 lumbar punctures). In one SMA type 3 patient with a posterior spine fusion operation, several CT-assisted lumbar puncture attempts with interlaminar access were not successful because of extensive interlaminar ossification postoperatively. Successful application of the drug via lumbar puncture in this patient

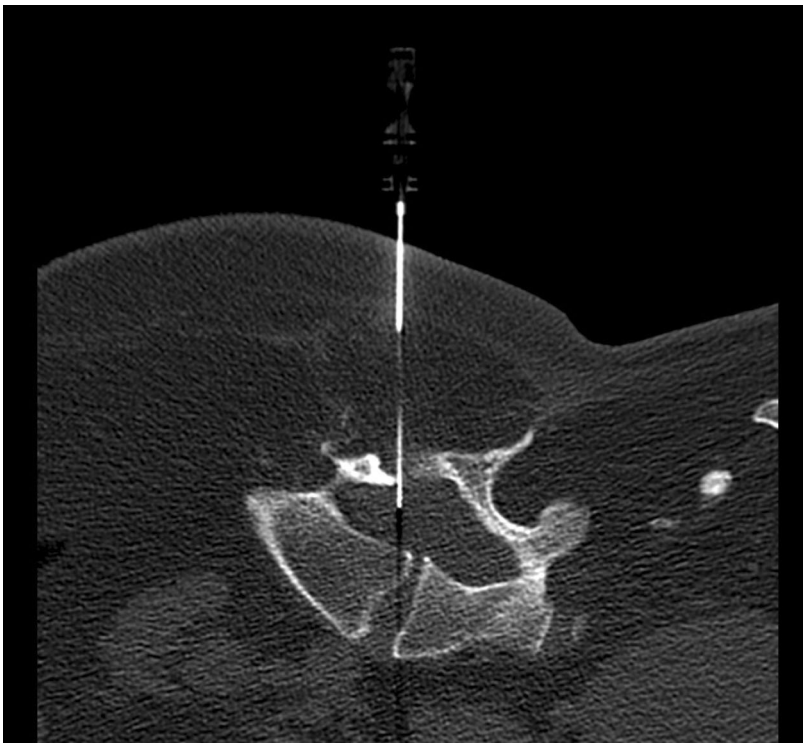

Fig. 2 Same patient as in Fig. 1. Axial image from CT demonstrates percutaneous paramedian interlaminar needle access L3/4 for the intrathecal administration of the drug

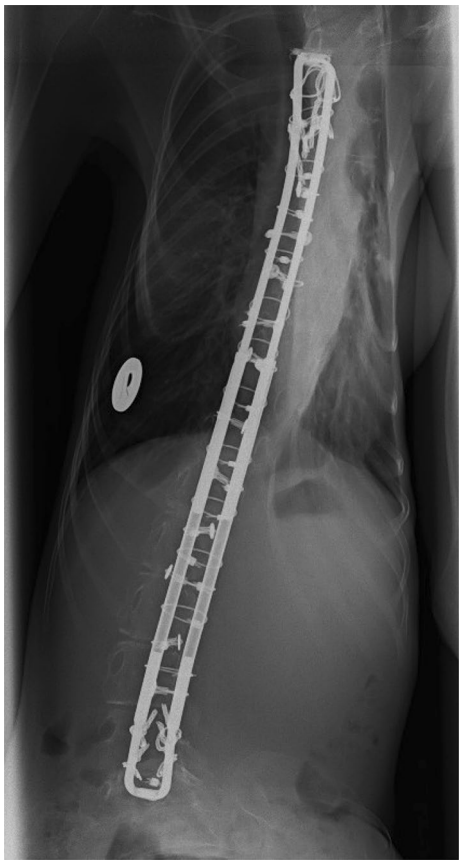

Fig. 3 CT-imaging shows the spine of a 13-year-old girl with type 2 spinal muscular atrophy before intrathecal administration of nusinersen. Scoliosis and posterior fusion instrumentation are shown here

was only possible with a right-sided transforaminal access at L4/5 (day 0 and day 28), L3/4 (day 14 and day 180) and L5/S1 (day 63) (Figs. 5, 6, 7). In two attempts, an epidural needle G18 with Tuohy cut was used; three lumbar punctures could be performed with a regular atraumatic 22G needle (Sprotte). In this patient, the first CSF was contaminated with blood after the first puncture (day 0), xanthochrome at the second injection (day 14), and the following times contaminated artificially with blood.

In general, length of needle insertion was 5.96 cm (SD 2.5 cm); CT-assisted 6.23 cm (SD 2.82 cm); conventional 5.54 cm (1.84 cm). Some data had to be estimated as accurate length measurement is not possible, especially in the conventional procedures.

Oxygen saturation did not differ before [mean 97.72% (SD 1.87%)] and after the intervention [mean 97.85% (SD 1.76%) ($p=0.108$)].

Three patients received regularly a premedication with lorazepam. Two of those patients needed additionally midazolam or in one intervention *S*-ketamine before the intervention. One patient solely received midazolam for all his interventions and one patient received regularly a combination of midazolam and *S*-ketamine. Dosage of lorazepam was between 0.5 and 1 mg (mean 0.81 mg, SD0.26 mg); dosage of midazolam was between 1 and 3 mg (mean 1.79 mg, SD 0.71 mg); dosage of *S*-ketamine was between 5 and 25 mg (mean 14.17 mg, SD 6.65 mg).

In 22 lumbar punctures (24%), no local anesthetic (either topic nor subcutaneous) was applied; in 33 lumbar punctures

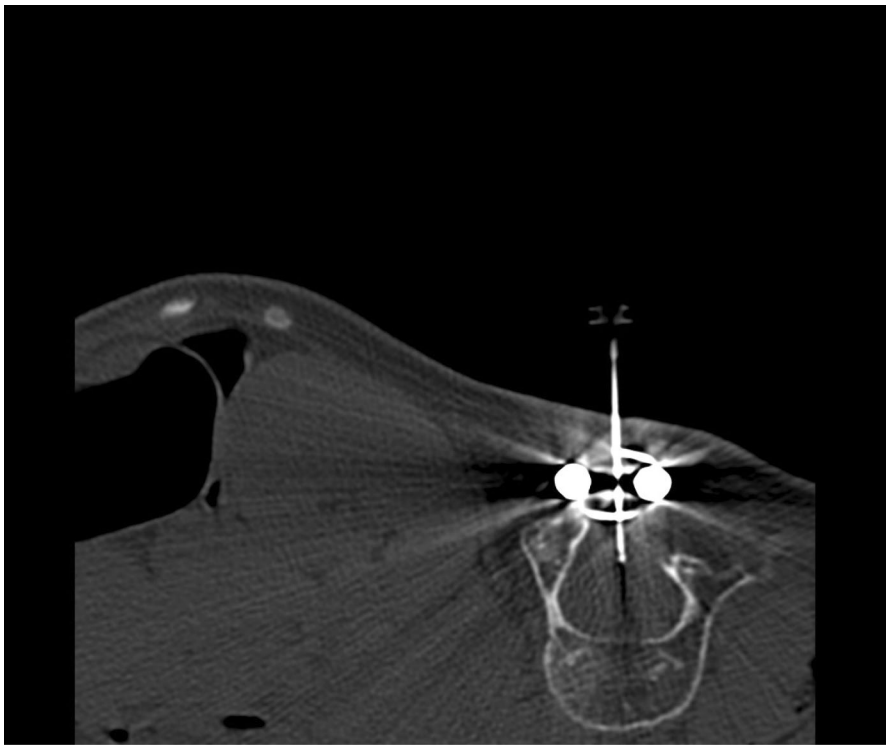

Fig. 4 Same patient as in Fig. 3. Axial CT demonstrates percutaneous posterior midline interlaminar access L3/4 for the intrathecal administration of the drug

(35%), solely topic anesthesia (lidocaine/prilocaine) were used; in 24 lumbar punctures (26%), we used subcutaneous anesthetics (mepivacaine); in 14 lumbar punctures (15%), we applied both, topic and subcutaneous anesthetics.

Mean X-ray dosage (indicated as dosage-length product) in patients with CT-assisted procedures was 85.6 mGy cm (SD 124.47 mGy cm, range 9–892 mGy cm).

In 52 of the 93 lumbar punctures, CSF was macroscopically clear (56%), in 39 artificially contaminated with blood (42%), in one lumbar puncture contaminated with blood (1%), and in the same patient in the following lumbar puncture xanthochrome (1%) (see above).

We observed 5 adverse events related to lumbar punctures in 3 of the 20 patients (all SMA type 3, ambulatory) in terms of a post-lumbar puncture syndrome with positional headache as main symptom 2–3 days after lumbar puncture. In two of these three patients, the headache occurred after the first and second lumbar puncture (day 0 and 14) and lasted 3–4 days and was less pronounced after the second puncture. One of these three patients additionally reported from lumbar backpain after the second puncture, lasting for 2 days. In one patient, positional headache was reported only after the second lumbar puncture (day 14) that however, lasted 7 days and was initially accompanied by nausea and vomiting for 2 days. In this patient, we tried to prevent a second post-lumbar puncture syndrome using an atraumatic 24G needle (Sprotte) during the next procedure (day 28). Since the application of the drug was clearly hampered by the smaller diameter of the needle in this case, we have not longer used this needle size. Apart from post-lumbar puncture syndrome, one patient developed a mild vasovagal reaction during lumbar puncture. Notably, we did not observe severe complications such as meningitis or hydrocephalus and none of the patients discontinued therapy. Details of lumbar puncture procedures are summarized in Table 2.

Discussion

The approval of the antisense oligonucleotide nusinersen by the FDA in December 2016 and the EMA in June 2017 represents a major step for the treatment of SMA. Nevertheless, treatment with nusinersen is challenging considering the clinical phenotype of the disorder and the route of administration of the antisense drug.

In this paper, we focus on the intrathecal administration of nusinersen in adolescent and adult late-onset patients (SMA type 2 and 3) in which a (roto)scoliosis, previous spine fusion operations, as well as joint contractures and respiratory insufficiency are frequently observed and make lumbar punctures complicated. In the previous studies, particularly in the initial trials, authors pointed on the challenges in drug administration due to complex anatomy, but sill observed an overall high technical success rate [18, 26]. In this study, lumbar puncture for the administration of nusinersen was possible in all 20 patients and 93 attempts. In eight patients without spinal deformities, a conventional lumbar puncture without imaging guidance was carried out.

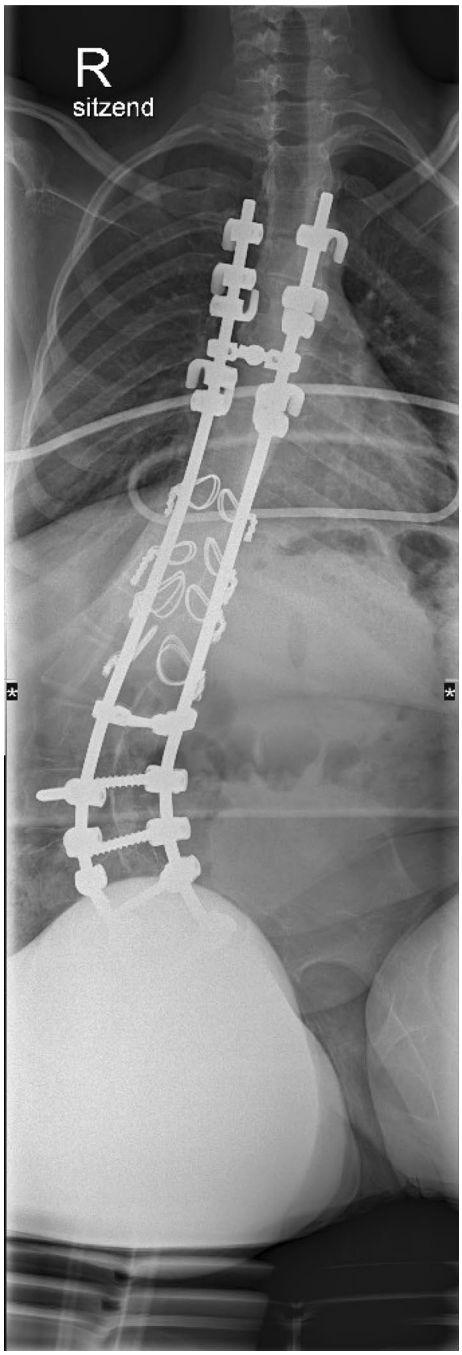

Fig. 5 X-ray-imaging shows the spine of a 13-year-old girl with type 3 spinal muscular atrophy before intrathecal administration of nusinersen. Scoliosis and extensive posterior fusion instrumentation are shown here

In none of the 11 patients with severe scoliosis or previous spine fusion operation, successful lumbar puncture was performed without CT-guidance. Furthermore, imaging support was necessary in one patient not due to scoliosis but due to obesity which prevented a conventional lumbar puncture attempt.

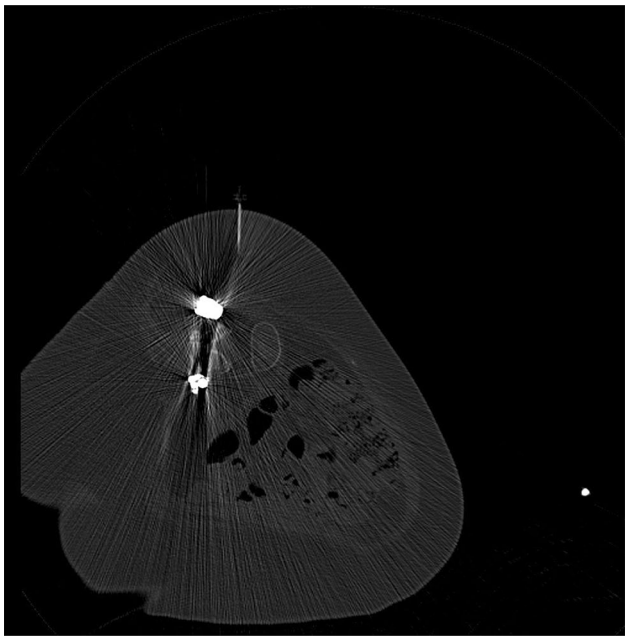

Fig. 6 Same patient as in Fig. 5. Axial CT demonstrates right-sided transforaminal L3/4 access for the intrathecal administration of the drug

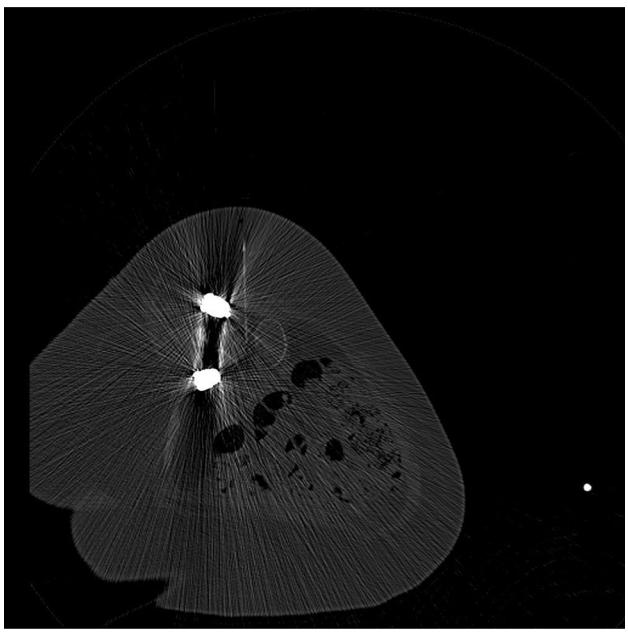

Fig. 7 Same patient as in Fig. 5. Axial CT demonstrates right-sided transforaminal L3/4 access for the intrathecal administration of the drug

In general, various imaging techniques can be used to facilitate lumbar puncture such as ultrasound, fluoroscopy, or CT. Ultrasound can simplify lumbar punctures [27] and is favored due to lack of radiation exposure over fluoroscopy

Table 2 Details of lumbar punctures ($N=93$)

	Patients		
	Total	CT-assisted	Conventional
Lumbar punctures	93	57 (61%)	36 (39%)
Trials (SD; range)	1.44 (1.16; 1–6)	1.16 (0.7; 1–6)	1.79 (1.34; 1–6)
Duration in min (SD; range)	37.29 (17.69; 20–150)	41.98 (19.88; 30–150)	29.86 (9.89; 20–45)
Position			
Prone	57 (61%)	57 (100%)	0 (0%)
Sitting	31 (33%)	0 (0%)	31 (86%)
Side	5 (5%)	0 (0%)	5 (14%)
Specialty			
Neurologist	36 (39%)	0 (0%)	36 (100%)
Orthopedic surgeon	40 (43%)	40 (70%)	0 (0%)
Neuroradiologist	17 (18%)	17 (30%)	0 (0%)
Length in cm (SD; range)	5.96 (2.5; 3–12)	6.23 (2.82; 3–12)	5.54 (1.84; 3.5–9)
Site			
L2/3	17 (18%)	13 (23%)	4 (11%)
L3/4	47 (51%)	23 (40%)	24 (67%)
L4/5	23 (25%)	15 (26%)	8 (22%)
L5/S1	6 (6%)	6 (11%)	0 (0%)
Sedation			
None	69 (74%)	36 (63%)	33 (92%)
Midazolam	10 (11%)	10 (18%)	0 (0%)
Lorazepam	5 (5%)	2 (4%)	3 (8%)
Midazolam/ketanest	6 (6%)	6 (11%)	0 (0%)
Midazolam/lorazepam	3 (3%)	3 (5%)	0 (0%)
Sedation (dosage) in mg (SD; range)			
Midazolam	1.79 (SD 0.71; 1–3)		
Lorazepam	0.81 (SD 0.26; 0.5–1)		
Ketanest	14.17 (SD 6.65; 5–25)		
Anesthesia local			
None	22 (24%)	9 (16%)	13 (36%)
Topic	33 (35%)	28 (49%)	5 (14%)
Infiltration	24 (26%)	6 (11%)	18 (50%)
Topic/infiltration	14 (15%)	14 (25%)	0 (0%)
NIV	28 (30%)	28 (49%)	0 (0%)
Oxygen saturation in %			
Before intervention	97.72 (SD 1,87; 92–100)	97.56 (SD1.56; 94–100)	97.97 (SD 2.29; 92–100)
After intervention	97.85 (SD 1,76; 93–100)	97.82 (SD1.56; 95–100)	97.89 (SD 2.05; 93–100)
Dose-length product (in mGy cm) (SD; range)	85.60 (SD 124.47; 9–892)	85.60 (SD 124.47; 9–892)	
CSF (macroscopic)			
Clear	52 (56%)	28 (49%)	24 (67%)
Artificially bloody	39 (42%)	27 (47%)	12 (33%)
Bloody	1 (1%)	1 (2%)	0 (0%)
Xanthochrome	1 (1%)	1 (2%)	0 (0%)
Complications			
Post-lumbar syndrome (events)	5 (5%)		
Mild vasovagal reaction	1 (1%)		

N number, *CT* computer tomography, *SD* standard deviation, *min* minutes, *cm* centimeter, *L2/3* between the second and third lumbar vertebra, *L3/4* between the third and fourth lumbar vertebra, *L4/5* between the fourth and fifth lumbar vertebra, *L5/S1* between the fifth lumbar vertebra and the first sacral vertebra, *mg* milligram, *NIV* non-invasive ventilation

and CT, in particular in children [28]. However, ultrasound is susceptible to artifacts from graft materials and image quality is reduced at increased target depths. Therefore, we did not use it in our patients. The utility of fluoroscopy has been well documented in a range of interventional radiology procedures including lumbar puncture [29] and has been used to facilitate lumbar puncture for the injection of nusinersen in SMA patients [18, 23]. In own experience, CT is superior in needle placement compared to fluoroscopy in difficult anatomical conditions, particularly in patients with posterior spinal hardware. Thus, we chose CT as a mean of imaging to facilitate lumbar punctures in patients with scoliosis and/or posterior spine fusions.

Formally, the product information of nusinersen specifies that the drug should be administered by means of lumbar puncture; but to get access to the subarachnoid space different approaches can be taken, for example posterior midline (interspinous) or paramedian interlaminar routes, which are standard, but also transforaminal approaches in the lumbar region or a caudal approach [19]. Further potential puncture sites are suboccipital via a medial cisternal access at the lower edge of the occiput [30] and cervicolateral between C1/C2 [31]. Both techniques carry risks, in particular of accidental puncture of the medulla oblongata or cervical vessels. In patients without spinal deformities, we used the standard access in the posterior midline (interspinous) between L2/3 and L4/5. In CT-guided lumbar punctures, we used a paramedian or posterior midline interlaminar access between L2/3 and L5/S1; only in one patient with a previous definitive posterior spine fusion operation and extensive posterior ossification [32], we had to use a transforaminal access for the intrathecal administration of the drug. So far, transforaminal routes have been described especially for epidural medication delivery [33]. However, fluoroscopy- or CT-guided transforaminal access routes have been already used in SMA patients for the administration of nusinersen in the previous published studies where aberrant spine anatomies precluding standard posterior lumbar puncture techniques [19–21]. Only in one patient, radicular pain after the procedure that resolved with conservative treatment was reported [21], so the authors described the transforaminal intrathecal access to be a safe, effective method for patients with spinal abnormalities. This is in line with our experience, although the first attempt using a transforaminal access was accompanied by a blood-contaminated CSF indicating a traumatic puncture. Moreover, besides transforaminal punctures in the lumbar region, even lateral C1/C2 and suboccipital punctures utilizing fluoroscopic guidance have been described in a few patients for the administration of nusinersen [22, 23]. Some authors concluded that cervical puncture is a feasible alternative delivery route to administer intrathecal nusinersen in patients with SMA and spine anatomy precluding lumbar access when done by providers with expertise in this procedure [22]. Other authors switched from cervical punctures to transforaminal punctures in the lumbar region after implementing the transforaminal approach in their center and recommended an algorithm using the cervical approach only if transforaminal and before that interspinous approaches failed [23].

Utility of CT and fluoroscopy regardless of the access route to subarachnoid space has obvious disadvantages, above all radiation exposure. X-ray-exposure ranged from 9 to 892 mGy cm for the interventions in our patients with a mean exposure of 89 mGy cm. Using the X-ray risk calculator (http://www.xrayrisk.com/index.php), we tried to estimate an additional cancer risk in our data due to radiation exposure, assuming that all punctures in one subject have to be carried out by CT-guidance and a treatment period of 2 years (6 lumbar punctures in year 1 and 3 lumbar punctures in year 2). Considering a mean age of 33.0 years in females and 25.8 years in males that received CT-guided lumbar punctures and corresponding mean dose-length products (DLP), we revealed an additional cancer risk due to radiation between 0.06–0.2%. Of note, the additional risks may individually vary up to 1%, e.g., in our youngest female with the highest DLP. However, these estimations have to be regarded with caution considering that using CT dose index or conversion coefficients as provided by [34] are likely to overestimate the dose in interventional procedures by as much as twofold [35–38]. Nevertheless, considering the additional cancer risk from radiation in particular for children [39], patients and/or parents necessarily have to be aware of these, especially when multiple CT-guided lumbar punctures are required. Thus, in these cases, we strongly recommend the inclusion of experts in radiology (and if necessary a physics) within the multidisciplinary team.

Besides radiation exposure, the required prone position for navigational overlay in the CT scanner is a further disadvantage. Lying in prone position can be challenging in later-onset SMA patients as scoliosis is often accompanied with significant joint contractures and/or joint dislocations. Particularly hip joint abnormalities required an extensive positioning on the CT table using blankets and pillows and were still often uncomfortable for the patient. Therefore, positioning on CT table was mostly done with the help of the parents or the personal assistants, who were trained in handling the patients. We did not observe significantly restricted thoracic excursions or significantly drop of oxygen saturation in prone position. During the procedure, all patients with respiratory insufficiency used NIV to ensure sufficient ventilation [17]. While another group recommended a tracheal intubation anesthesia for prone position [23], this was not necessary in our patients. As recommended in a previous study, we chose the most minimal dosage of sedative or anesthesia medications to permit safe and effective completion of the procedure [18]. Even with low-to-moderate dosages

of benzodiazepines (mean dosage of midazolam 1.79 mg, mean dosage of lorazepam 0.81 mg) and *S*-ketamine (mean dosage 14.17 mg), a sufficient sedation and anxiolysis was possible without respiratory distress. To reduce procedure-related pain and decrease the requirement for sedation, we used local anesthesia at the lumbar puncture site in form of a topic anesthetic cream which is common especially in pediatrics [17] and/or infiltrative subcutaneous anesthesia. To minimize the risk of post-lumbar puncture syndrome, we mainly used atraumatic needles [40]. However, post-lumbar puncture syndrome with and without vomiting was observed in three ambulatory SMA type 3 patients, in two repeatedly. Here, the main symptom reported was positional headache and patients were advised to take non-steroidal anti-inflammatory medication (NSAID, e.g., paracetamol) and to bed rest that lead to an attenuation of the symptoms. Of note, inpatient treatment or prolonged hospitalization was not necessary and none of the patients discontinued therapy due to post-lumbar puncture syndrome. In all these patients, lumbar puncture was performed with an atraumatic needle 22G (Sprotte). Besides needle design (traumatic versus atraumatic), post-lumbar puncture syndrome is related to the size of the spinal needle used, the experience of the performing person, and the age and sex of the patient [41]. The incidence of post-lumbar puncture syndrome in adults ranges from 0 to 36% (Quincke 22 G 36% [42], Sprotte 24 G 0–9.6% [41, 43, 44]), and in children from 4 to 11% [45, 46]. With puberty, the incidence of complaints after lumbar puncture, particularly of headache, increases [47]. Our results are in line with the previous studies where post-lumbar puncture syndrome during treatment with nusinersen was more often observed in older children (8–14 years of age) and in children with spinal muscular atrophy type 3 [18]. Most authors explained the higher incidence of post-lumbar puncture syndrome observed among older children and/or in children with spinal muscular atrophy type 3 with the use of larger bore/gauge spinal needles, cutting-tip needles (e.g. Quincke type), multiple attempts, and/or due to technical difficulties resulting from increased body weight and the presence of scoliosis or excessive lumbar lordosis, which was not the case in our patients. Using a needle with a smaller diameter (24G) in a patient with a previous post-lumbar puncture syndrome led to a higher resistance when aspiring CSF and injecting nusinersen, so we did not adjust standard use of this needle diameter [41]. Apart from post-puncture syndrome and a single mild vasovagal reaction in a conventional lumbar puncture, no serious side effects occurred during the procedures.

Our data suggest that nusinersen can be successfully administered even in patients with complex anatomies and severe illness within a multidisciplinary approach. However, we may also assume a limited feasibility of lumbar puncture for drug application in some cases. In detail, e.g. (postoperative) fistula or other expansive lesions within the route of needle insertion, or extensive interlaminar ossifications in combination with inaccessible neuroforamina may represent potential limitations. In addition, artifacts arising from previously implanted surgery material may also restrict imaging-guided drug application.

Despite focusing on drug administration, we assessed HFMSE scores before and after four doses of nusinersen (loading) and found no significant improvements in motor functions. We did not assess subjective drug efficacy or subjective effort versus effectiveness consideration but however, none of the 20 patients discontinued therapy. Nevertheless, it is of note that our study is not eligible to assess drug efficacy, but, considering the age and illness duration in our sample, our result on HFMSE scores is in line with the observation that the earlier SMN levels were augmented, the better the therapeutic outcome [8, 48]. A significant improvement in motor functions was found in children even with later-onset SMA [10], but, however, there is no study that investigated the efficacy of nusinersen in adolescents or adults so far. Studies addressing this issue are strongly encouraged considering that these evidences would strongly support the essential evaluation between risks versus efficacy in clinical practice. Moreover, these data would also make a strong contribution to the ongoing discussion regarding costs and the implications on national health systems [49] considering the current drug prizes and efforts due to drug administration.

Conclusions

Overall, we conclude that the conventional or CT-guided lumbar puncture for the administration of nusinersen in adolescent and adult later-onset SMA patients even with complex anatomies and respiratory insufficiency is feasible, safe, and well tolerated. CT-guided lumbar puncture in complex spine anatomies required not more puncture attempts compared to the conventionally performed lumbar punctures in patients without spine deformities. In summary, the use of imaging facilitates the procedure and increases the success of intrathecal medication delivery in patients with spine deformities. To further reduce X-ray exposure, the utility of fluoroscopy instead of CT can be considered. Only local anesthesia and mild sedation with benzodiazepines and ketamine were used during the procedures. To ensure a safe intervention, we recommend establishing an experienced interdisciplinary team consisting of neurologists, neuropediatricians, anesthesiologists, orthopedic surgeons, and neuroradiologists.

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Compliance with ethical standards

Conflicts of interest The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. CDW has received honoraria from Biogen as an advisory board member and for lectures and as a consultant from Hoffmann-La Roche. ACL has received financial research support from AB Science, Biogen Idec, Cytokinetics, GSK, Orion Pharam, Novartis, TauRx Therapeutics Ltd., and TEVA Pharmaceuticals, and has received honoraria as a consultant from Mitsubishi, Orion Pharma, Novartis, Teva and as an advisory board member from Biogen, Treeway, and Hoffmann-La Roche. ZU has received honoraria from Biogen as a consultant. BW has received honoraria from Biogen for a lecture. SW, KW, MS, RS, and TK report no disclosures relevant to the manuscript.

Ethical standards The study was approved by the local ethics committee and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Patients or their relatives gave informed consent to participate in the study.

Research data policy Demographic and clinical data on motor functions of the investigated patients are provided to the German Network for Motor Neuron Diseases (MND-NET).

References

1. Lunn MR, Wang CH (2008) Spinal muscular atrophy. Lancet 371:2120–2133. https://doi.org/10.1016/S0140-6736(08)60921-6
2. Lefebvre S, Bürglen L, Reboullet S et al (1995) Identification and characterization of a spinal muscular atrophy-determining gene. Cell 80:155–165. https://doi.org/10.1016/0092-8674(95)90460-3
3. Wang CH, Finkel RS, Bertini ES et al (2007) Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. https://doi.org/10.1177/0883073807305788
4. Mercuri E, Finkel RS, Muntoni F et al (2018) Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 28:103–115. https://doi.org/10.1016/j.nmd.2017.11.005
5. Finkel RS, Mercuri E, Meyer OH et al (2018) Diagnosis and management of spinal muscular atrophy: Part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord 28:197–207. https://doi.org/10.1016/j.nmd.2017.11.004
6. Passini MA, Bu J, Richards AM et al (2011) Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy. Sci Transl Med 3:72ra18–72ra18. https://doi.org/10.1126/scitranslmed.3001777
7. Singh NK, Singh NN, Androphy EJ, Singh RN (2006) Splicing of a critical exon of human survival motor neuron is regulated by a unique silencer element located in the last intron. Mol Cell Biol. https://doi.org/10.1128/MCB.26.4.1333-1346.2006
8. Hua Y, Sahashi K, Hung G et al (2010) Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. Genes Dev 24:1634–1644. https://doi.org/10.1101/gad.1941310
9. Finkel RS, Mercuri E, Darras BT et al (2017) Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 377:1723–1732. https://doi.org/10.1056/NEJMoa1702752
10. Mercuri E, Darras BT, Chiriboga CA et al (2018) Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. https://doi.org/10.1056/NEJMoa1710504
11. Bertini E, Hwu W-L, Reyna SP et al (2017) Efficacy and safety of nusinersen in infants with presymptomatic spinal muscular atrophy (SMA): interim results from the NURTURE study. Eur J Paediatr Neurol 21:e14. https://doi.org/10.1016/j.ejpn.2017.04.1218
12. Schwentker EP, Gibson DA (1976) The orthopaedic aspects of spinal muscular atrophy. J Bone Jt Surg Ser A
13. McElroy MJ, Shaner AC, Crawford TO et al (2011) Growing rods for scoliosis in spinal muscular atrophy. Spine (Phila Pa 1976). https://doi.org/10.1097/BRS.0b013e3182194937
14. Holt JB, Dolan LA, Weinstein SL (2017) Outcomes of primary posterior spinal fusion for scoliosis in spinal muscular atrophy. J Pediatr Orthop. https://doi.org/10.1097/BPO.0000000000001049
15. Phillips DP, Roye DP, Farcy JP et al (1990) Surgical treatment of scoliosis in a spinal muscular atrophy population. Spine (Phila Pa 1976)
16. Kaufmann P, McDermott MP, Darras BT et al (2011) Observational study of spinal muscular atrophy type 2 and 3: functional outcomes over 1 year. Arch Neurol. https://doi.org/10.1001/archneurol.2010.373
17. Pechmann A, Langer T, Wider S, Kirschner J (2017) Original article single-center experience with intrathecal administration of Nusinersen in children with spinal muscular atrophy type 1. Eur J Paediatr Neurol. https://doi.org/10.1016/j.ejpn.2017.11.001
18. Haché M, Swoboda KJ, Sethna N et al (2016) Intrathecal injections in children with spinal muscular atrophy: Nusinersen clinical trial experience. J Child Neurol 31:899–906. https://doi.org/10.1177/0883073815627882
19. Weaver JJ, Natarajan N, Shaw DWW et al (2018) Transforaminal intrathecal delivery of nusinersen using cone-beam computed tomography for children with spinal muscular atrophy and extensive surgical instrumentation: early results of technical success and safety. Pediatr Radiol. https://doi.org/10.1007/s00247-017-4031-6
20. Geraci AP, Black K, Jin M et al (2018) Transforaminal lumbar puncture for intrathecal nusinersen administration. Muscle Nerve. https://doi.org/10.1002/mus.26082
21. Nascene DR, Ozutemiz C, Estby H et al (2018) Transforaminal lumbar puncture: an alternative technique in patients with challenging access. Am J Neuroradiol. https://doi.org/10.3174/ajnr.A5596
22. Veerapandiyan A, Pal R, D'Ambrosio S et al (2018) Cervical puncture to deliver nusinersen in patients with spinal muscular atrophy. Neurology. https://doi.org/10.1212/WNL.0000000000006006
23. Mousa MA, Aria DJ, Schaefer CM et al (2018) A comprehensive institutional overview of intrathecal nusinersen injections for spinal muscular atrophy
24. O'Hagen JM, Glanzman AM, McDermott MP et al (2007) An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord. https://doi.org/10.1016/j.nmd.2007.05.009
25. Glanzman AM, O'Hagen J, McDermott M et al (2011) Validation of the expanded hammersmith functional motor scale in spinal muscular atrophy type II and III. J Child Neurol. https://doi.org/10.1177/0883073811420294
26. Chiriboga CA, Swoboda KJ, Darras BT et al (2016) Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. Neurology 86:890–897. https://doi.org/10.1212/WNL.0000000000002445
27. Dussourd L, Martinon B, Candille C et al (2017) Ultrasonography helps emergency physician identify the best lumbar puncture site under the conus medullaris. Scand J Trauma Resusc Emerg Med

28. Pierce DB, Shivaram G, Koo KSH et al (2018) Ultrasound-guided lumbar puncture in pediatric patients: technical success and safety. Pediatr Radiol. https://doi.org/10.1007/s00247-018-4091-2
29. Cauley KA (2015) Fluoroscopically guided lumbar puncture. Am J Roentgenol. https://doi.org/10.2214/AJR.14.14028
30. Loebe FM (1988) History and significance of suboccipital puncture. Psychiatr Neurol Med Psychol (Leipz) 40:617–620
31. Knosp E, Richling B, Horaczek A (1984) Laterale C1/C2-Punktion: Darstellung der Technik und Ergebnisse der ersten 100 Patienten. Acta Chir Austr 16:81–84. https://doi.org/10.1007/BF02656232
32. Cahill PJ, Marvil S, Cuddihy L et al (2010) Autofusion in the immature spine treated with growing rods. Spine (Phila Pa 1976). https://doi.org/10.1097/BRS.0b013e3181e21b50
33. Andreisek G, Jenni M, Klingler D et al (2013) Access routes and reported decision criteria for lumbar epidural drug injections: a systematic literature review. Skelet Radiol. https://doi.org/10.1007/s00256-013-1713-5
34. Huda W, Ogden KM, Khorasani MR (2008) Converting dose-length product to effective dose at CT. Radiology. https://doi.org/10.1148/radiol.2483071964
35. Chang AL, Schoenfeld AH, Brook AL, Miller TS (2013) Radiation dose for 345 CT-guided interlaminar lumbar epidural steroid injections. Am J Neuroradiol. https://doi.org/10.3174/ajnr.A3540
36. Bauhs JA, Vrieze TJ, Primak AN et al (2008) CT dosimetry: comparison of measurement techniques and devices. RadioGraphics. https://doi.org/10.1148/rg.281075024
37. Leng S, Christner JA, Carlson SK et al (2011) Radiation dose levels for interventional CT procedures. Am J Roentgenol. https://doi.org/10.2214/AJR.10.5057
38. Lazarus MS, Forman RB, Brook AL, Miller TS (2017) Radiation dose and procedure time for 994 CT-guided spine pain control procedures. Pain Physician
39. Pearce MS, Salotti JA, Little MP et al (2012) Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. https://doi.org/10.1016/S0140-6736(12)60815-0
40. Thomas SR, Jamieson DR, Muir KW et al (2000) Randomised controlled trial of atraumatic versus standard needles for diagnostic lumbar puncture. BMJ. https://doi.org/10.1136/bmj.321.7267.986
41. Turnbull DK, Shepherd DB (2003) Post-dural puncture headache: pathogenesis, prevention and treatment. Br J Anaesth 91:718–729. https://doi.org/10.1093/bja/aeg231
42. Tourtellotte WW, Henderson WG, Tucker RP et al (1972) A randomized, double-blind clinical trial comparing the 22 versus 26 gauge needle in the production of the post-lumbar puncture syndrome in normal individuals. Headache J Head Face Pain. https://doi.org/10.1111/j.1526-4610.1972.hed1202073.x
43. Campbell DC, Douglas MJ, Pavy TJG et al (1993) Comparison of the 25-gauge Whitacre with the 24-gauge Sprotte spinal needle for elective Caesarean section: cost implications. Can J Anaesth. https://doi.org/10.1007/BF03009601
44. Ross AW, Greenhalgh C, McGlade DP et al (1993) The sprotte needle and post dural puncture headache following Caesarean section. Anaesth Intensive Care
45. Lowery S, Oliver A (2008) Incidence of postdural puncture headache and backache following diagnostic/therapeutic lumbar puncture using a 22G cutting spinal needle, and after introduction of a 25G pencil point spinal needle. Paediatr Anaesth. https://doi.org/10.1111/j.1460-9592.2008.02414.x
46. Janssens E, Aerssens P, Alliët P et al (2003) Post-dural puncture headaches in children. A literature review. Eur J Pediatr. https://doi.org/10.1007/s00431-002-1122-6
47. Ebinger F, Kosel C, Pietz J, Rating D (2004) Headache and backache after lumbar puncture in children and adolescents: a prospective study. Pediatrics. https://doi.org/10.1542/peds.113.6.1588
48. Zhou H, Meng J, Marrosu E et al (2015) Repeated low doses of morpholino antisense oligomer: an intermediate mouse model of spinal muscular atrophy to explore the window of therapeutic response. Hum Mol Genet 24:6265–6277. https://doi.org/10.1093/hmg/ddv329
49. The Lancet Neurology (2017) Treating rare disorders: time to act on unfair prices. Lancet Neurol 16:761