Elderly Patient with 5q Spinal Muscular Atrophy Type 4 Markedly Improved by Nusinersen

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Highlights:

- We report a 71-year-old Japanese woman with 5q spinal muscular atrophy type 4.
- Her muscle weakness improved after intrathecal treatment with nusinersen.
- Intrathecal treatment with nusinersen might improve muscle weakness even in patients with adult-onset elderly 5q spinal muscular atrophy.

Dear Editor,

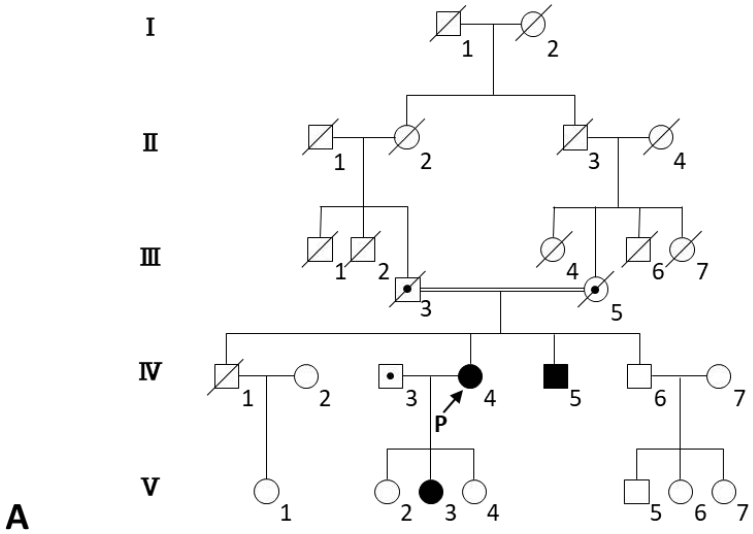
5q Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by homozygous deletions or variants in the *survival motor neuron 1 (SMN1)* gene encoding the survival motor neuron (SMN) protein. Decreased level of SMN protein results in lower motor neuron degeneration, muscle atrophy, and weakness (1, 2). A paralogous gene, *survival motor neuron 2 (SMN2)*, also encodes SMN protein; however, approximately 90% of the *SMN2* gene transcripts result in truncated non-functional SMN protein and only 10% result in full-length SMN, which is insufficient to prevent the disease (2, 3). Based on onset age and disease severity, SMA is classified into four clinical types—severe type 1 (SMA1, OMIM 253300), moderate type 2 (SMA2, OMIM 253550), mild type 3 (SMA3, OMIM 253400), and adult-onset type 4 (SMA4, OMIM 271150) (4). SMA type 4 is rare and only a few number of cases have been reported till date (5).

Nusinersen, an antisense oligonucleotide therapeutic drug, inhibits splicing factors in the *SMN2* gene and increases the amount of full-length SMN protein (6). In recent clinical trials, intrathecal treatment with nusinersen has shown a significant effect on motor development, function, and survival in infants and children with 5q SMA type 1, 2, or 3 (7, 8). However, limited information is available regarding the clinical benefits of nusinersen in elderly patients, and only one case of 5q SMA type 4 treated with nusinersen has been reported thus far (9). Here, we report on an elderly Japanese patient with 5q SMA type 4, whose motor functions were markedly improved by intrathecal treatment with nusinersen.

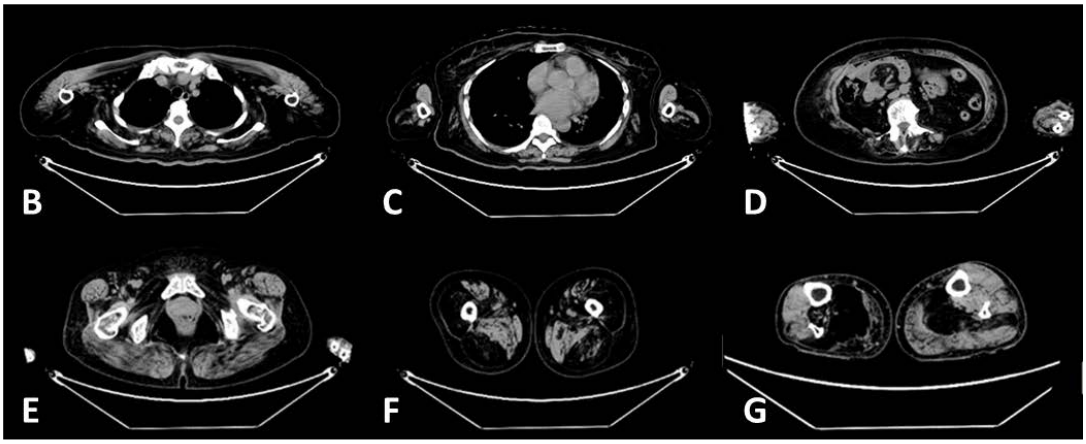
Case Report

The patient (IV-4), a 71-year-old Japanese woman, was born to consanguineous parents (Supplementary Figure 1A).

Supplementary Figure 1



A



Her younger brother (IV-5) and second daughter (V-3) were diagnosed with 5q SMA type 3. She had a medical history of type 2 diabetes mellitus. She did not notice any motor problems up to the age of 46 when she first experienced difficulty in climbing stairs and weakness of extremities, and these symptoms gradually deteriorated. At the age of 51 years, she visited the Department of Neurology, Shinshu University Hospital. A neurological examination revealed proximal dominant muscle atrophy and weakness in her extremities; however, there were no abnormal findings in the cranial nerves. The tendon reflexes were decreased, and both Babinski and Chaddock signs were absent on both sides. She walked with a positive Trendelenburg sign. A needle electromyogram showed high amplitude and long-duration motor units with a late recruitment pattern in her limbs; however, these changes were not seen in the cranial muscles, including the tongue. Both motor and sensory conduction velocities were normal; however, compound muscle action potential in her lower extremities was reduced in amplitude. Muscle computed tomography showed atrophy of the shoulder girdle and upper leg muscles (Supplementary Figure 1B-G). At age of 68 years, she started requiring assistance for walking with a cane.

A multiplex ligation-dependent probe amplification analysis of *SMN1* and *SMN2* was performed, as the clinical findings of the patient were suggestive of SMA, after informed consent was obtained from the patient. DNA was extracted from the peripheral leukocytes of the patient according to the standard protocol. Genetic testing revealed a homozygous loss of exon 7 and 8 of *SMN1* with 4 copy numbers for exon 7 and 8 of *SMN2*. At the age of 71 years, intrathecal treatment with nusinersen was initiated following standard protocol. Her gait just before nusinersen administration is shown in Supplemental video 1. Her fatigability and muscle weakness gradually improved after the initial administration of nusinersen, and she became capable of walking without the assistance of a cane after three months of the first administration of nusinersen (Supplemental video 2). Results of the Timed Up and Go Test, Barthel Index, and Hammersmith Functional Motor

Scale-Expanded (HFMSE) are summarized in Table 1.

Table 1. Time course of the Timed Up and Go Test, Barthel Index, and HFMSE before and after intrathecal treatment with nusinersen

	Before	After 4 weeks	After 12 weeks	After 39 weeks	After 65 weeks	After 90 weeks
Timed Up and Go Test (sec)	19.6	18.0	12.6	13.0	12	15
Barthel Index (point)	90	90	100	100	100	100
HFMSE	n.e.	36	45	45	46	42

HFMSE, Hammersmith Fuctional Motor Scale-Expanded; n.e., not examined

Discussion

Clinically, SMA type 4 encompasses heterogeneous patients showing adult-onset slowly progressive lower motor neuron disease. Actually, it was reported that majority of patients with SMA type 4 phenotype had no deletions in *SMN1* (10). The clinical manifestations in our case are characterized as adult-onset, relatively mild muscle involvement, and slow progression. The result of the patient`s genetic testing revealed a homozygous deletion in *SMN1* with 4 copies of *SMN2*. These clinical and genetic features are similar to those of the previously reported 5q SMA type 4 families (5). This case is the oldest patient treated with nusinersen.

The pharmacological effect of nusinersen in elderly or long-standing patients with 5q SMA needs to be elucidated. Hagenacker *et al*. have reported real-world data on the use of nusinersen in adult 5q SMA patients aged 16–65 years, showing significant improvements in HFMSE (9). Moreover, greater increase of HFMSE was observed in 5q SMA type 3 patients with 3 or 4 copies of *SMN2* (9). Our patient had 4 copy numbers, compatible with the aforementioned study by Hagenacker *et al* (9). Based on the pharmacological action of nusinersen, a greater effect of nusinersen in patients with higher *SMN2* copy numbers could be expected (7-9).

In addition to 5q SMA, *SMN2* copy number can act as a prognostic factor in amyotrophic lateral sclerosis.[10] Therefore, increasing the expression of *SMN2* may provide a common strategy for treatment of motor neuron diseases (11). Considering the disease pathogenesis of neurodegenerative diseases including 5q SMA, an early intervention is required for treatment. Moreover, recent clinical trials in children with 5q SMA have reported better motor response in patients with an earlier administration of nusinersen (7, 8). However, this patient showed marked improvement in motor functions shortly after administration of nusinersen therapy, despite a long-standing disease course. These findings indicate that the underlying surviving anterior cells in a non-functional but viable state were activated by nusinersen.

In conclusion, we report a clinical benefit of nusinersen in a patient with 5q SMA type 4, having a long-standing disease course. Our findings show that intrathecal treatment with nusinersen can improve muscle weakness even in patients with adult-onset elderly 5q SMA. Studies involving more number of patients are required to gain further insight into the management of 5q SMA type 4.

Conflict of interest

The authors have no conflict of interest to declare.

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Figure legends

Supplementary Figure 1. (A) Pedigree of the family. ■/●= affected individuals; / = deceased; → = proband. (B-G) Muscle CT images. Muscles of shoulder girdle (C) and upper leg muscles (F) had dominantly fatty atrophic change.

Video legends

Video 1. (A) Patient (IV-4) showed marked walking disability with a Trendelenburg's sign due to proximal dominant muscle weakness in her lower limbs.

Video 2. At 8 months after administration of Intrathecal treatment with nusinersen, patient (IV-4) showed improvement in walking and became capable of walking without a cane.