SPINAL MUSCULAR ATROPHY

Genetic Counseling Webinar: Case Reports On Rare Disease

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Veronica Wulan W.

Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada

Introduction

Spinal Muscular Atrophy (SMA)

SMA is an autosomal recessive neuromuscular condition characterized by the degeneration of motor neurons in the spinal cord. [1]

The estimated incidence of the disorder is 1 in 6.000–11.000 neonates, with a carrier frequency of 1 in 40–67. [2]

1. Nurputra D, et al. Spinal Muscular Atrophy: From Gene Discovery to Clinical Trials. Annals of Human Genetics. 2013;77(5):435-463.
2. Reed U, Zanoteli E. Therapeutic advances in 5q-linked spinal muscular atrophy. Arquivos de Neuro-Psiquiatria. 2018;76(4):265-272.

Introduction

The majority of SMA cases are caused by mutations in the survival motor neuron 1 (SMN1) gene, which is located on chromosome 5q13. [3]

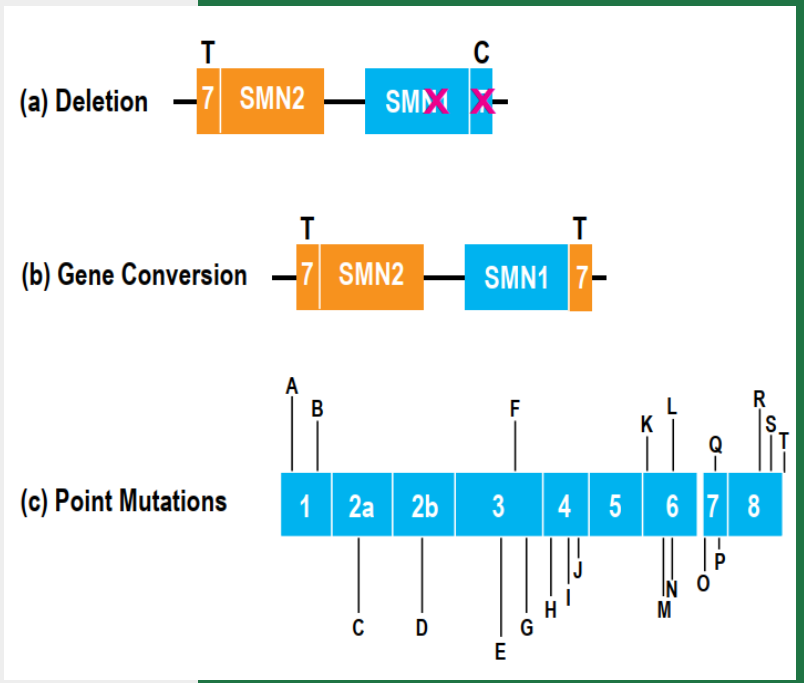
95%

Mutation [3] :

- Homozygous deletion of SMN1 exon 7 or gene conversion from SMN1 to SMN2

5%

- Compound heterozygotes for an SMN1 exon 7 deletion and an SMN1 point mutation



3. Keinath M, Prior D, Prior T. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. The Application of Clinical Genetics. 2021;Volume 14:11-25.

CASE REPORT

A 15-years-old female was presented to pediatric outpatient clinic due to weakness and atrophy of all four extremities with chronic progressive onset since 1 year old.

HISTORY OF PRESENT ILLNESS

1 year old

- Patient began to fall frequently while walking
- Need help from others or have to hold on nearby objects when standing up again.

3-5 years old

- Patient began seeing the pediatrician and routine control until the age of 5 years.
- Complaints was persisted.
- Advised for muscle biopsy but the family refused.

11 years old

- Patient started using a wheelchair.

14 years old

- Patient still could not to stand and walk.
- Began to feel weak in both hands, especially when raising them, but still strong to hold objects.
- Patient felt all four extremities are smaller in size.
- Patient was seeing the pediatrician and had muscle biopsy

Muscle biopsy result:

- **possible for muscular dystrophy**

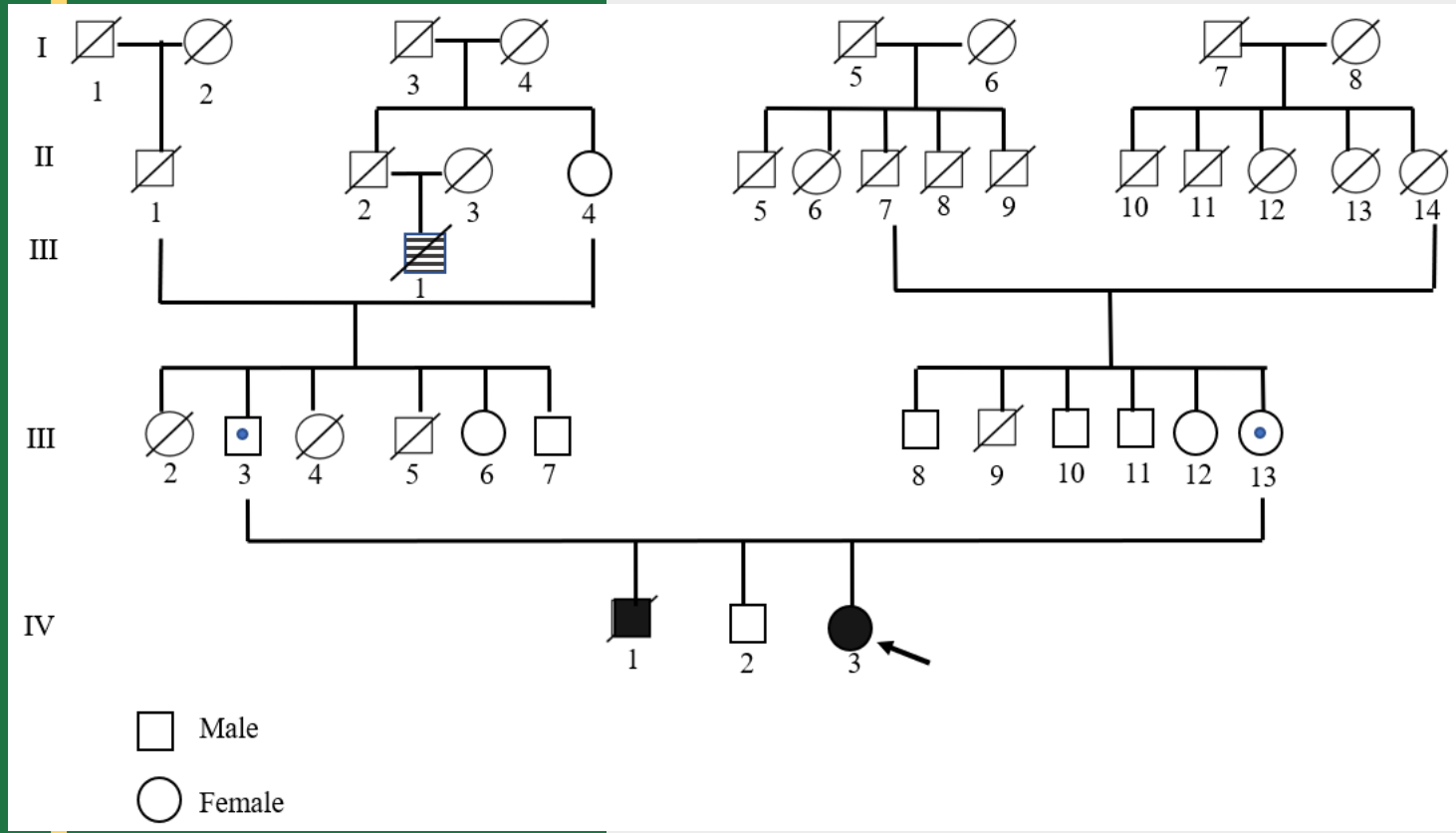
CK: 139 (26-192) U/L

15 years old

- Patient had genetic examination and diagnosed with Spinal Muscular Atrophy (SMA).

FAMILY HISTORY

- In this case, **patient [IV.3] had SMA**
- The **patient's older brother [IV.1]** suffered for same complaints, could stand at age of 1 year, could not walk at 2 years old and had died at 17 years-old.
- The **patient's great-grand father [III.1]** suffered right hemiparesis since childhood, could walk with assistance of walker aid device.

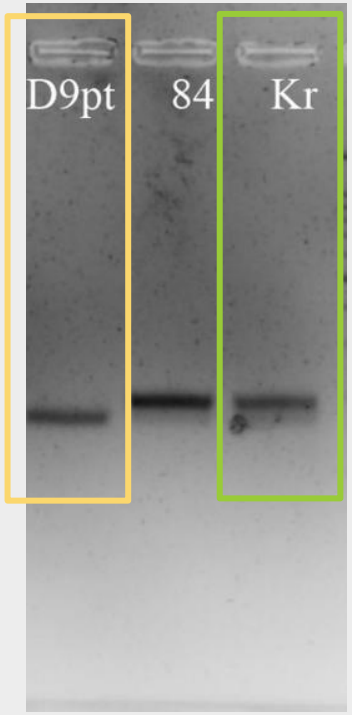


Genetic examination

PCR - Restriction Fragment Length Polymorphism (RFLP):

- **Deletion of exon 7 of SMN1 gene**

  → Spinal Muscular Atrophy



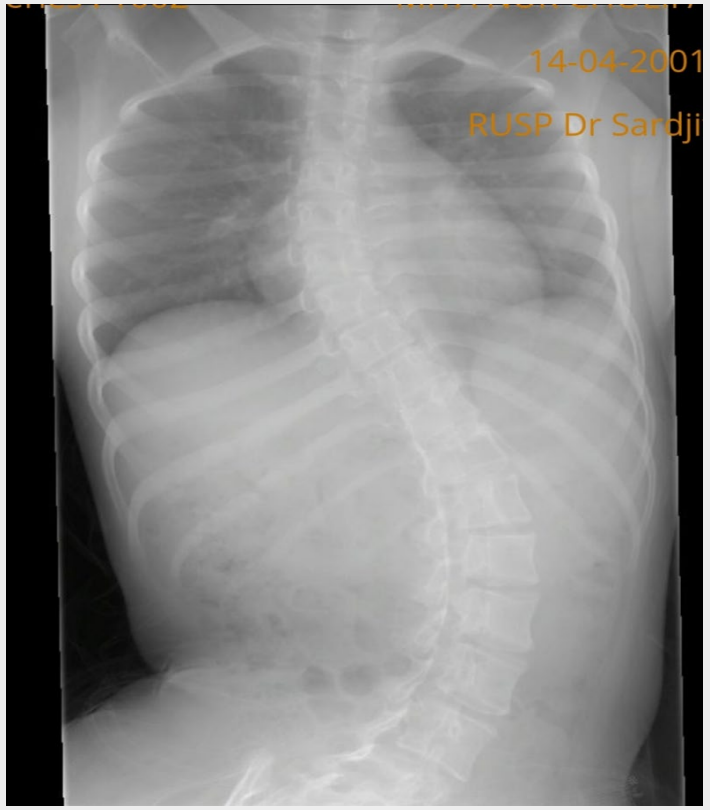
Patient Control

ENMG :

- Axonophatic lesion on left peroneus nerve and bilateral tibialis nerve.
- Support for lesion on anterior cornu medula spinalis
- Correspond to clinical compliance of Spinal Muscular Atrophy.

Ro Vertebra thoracolumbal:

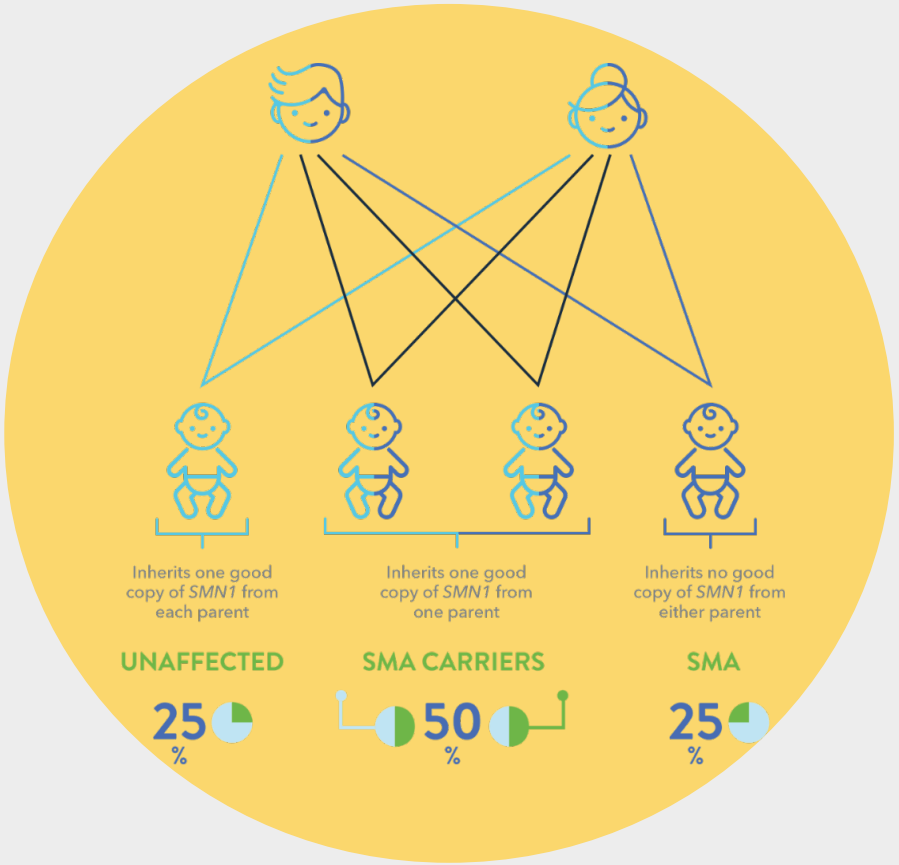
- Levoscoliosis thoracalis



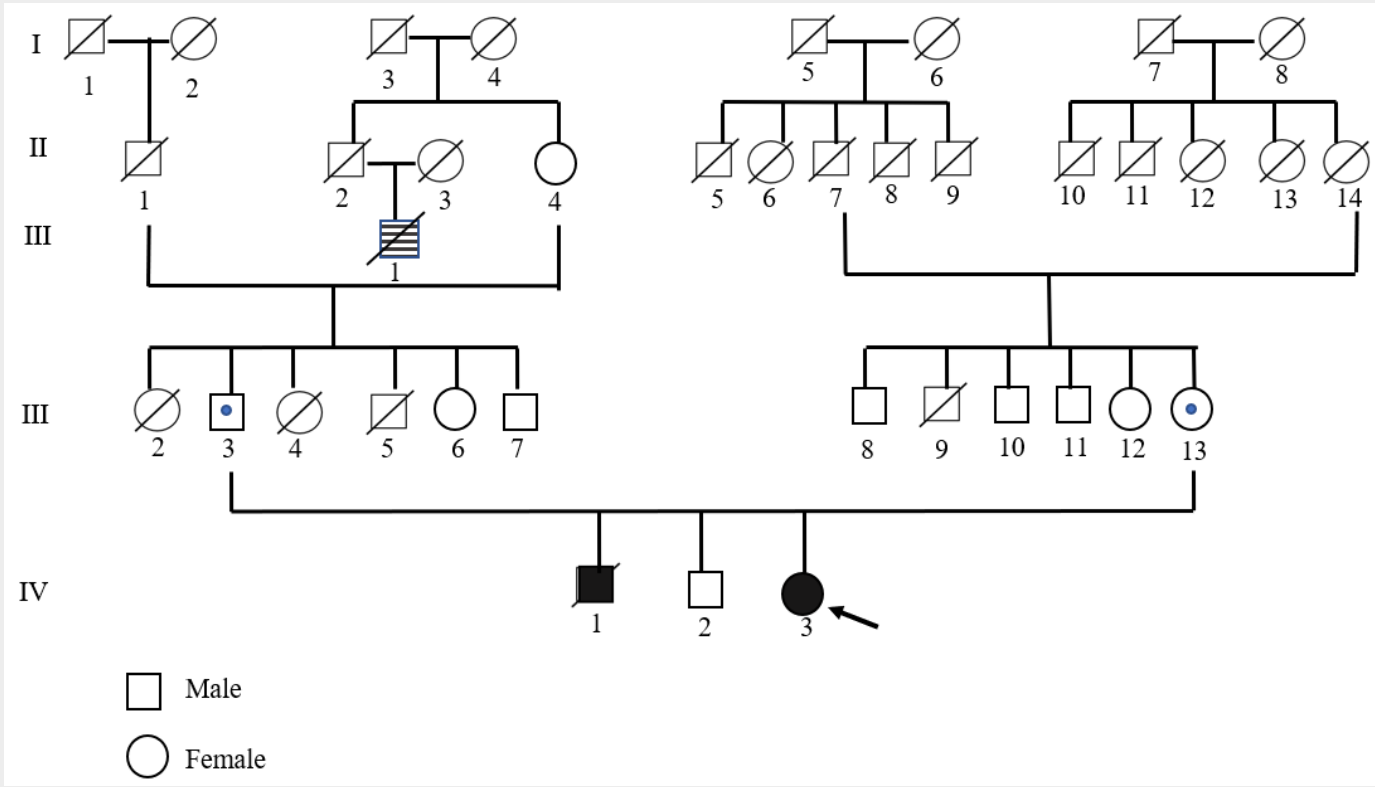
Final Diagnosis

Spinal Muscular Atrophy type 2

Discussion



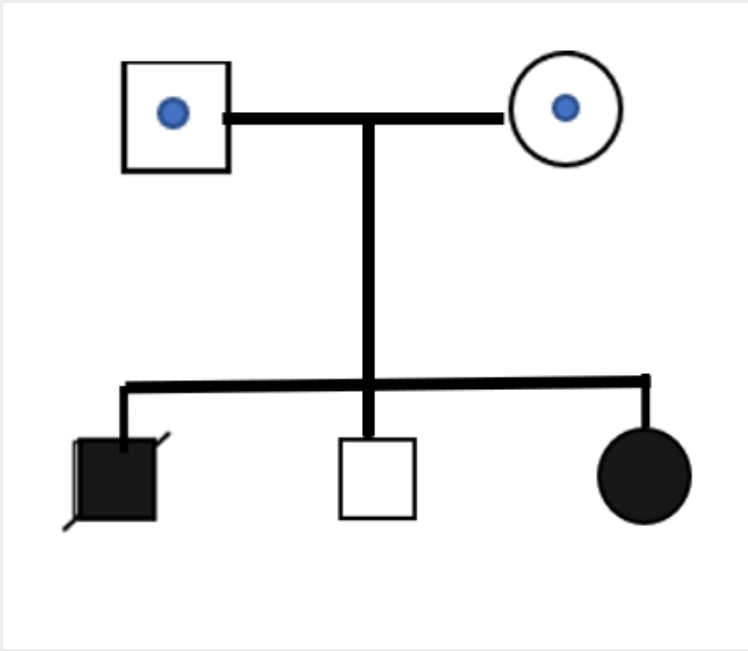
Family genetic testing is important and needed to determine family member status.



SMA in this case was highly possible inherited from carrier parents.

Discussion

- Father : carrier
- Mother : carrier
- 1st child : SMA
- 2nd child : 25% unaffected, 50% carrier
- 3rd child : SMA



Discussion

Type of Treatment	Mechanism of Action	Drug	Route of Administration	Clinical Trials	Current Status
SMN dependent pathway					
SMN1 gene delivery	*SMN1* gene transfer via adenovirus vector	Onasemnogene abeparvovec	Single intravenous injection	START (Phase I) STRONG (Phase I) SPR1NT (Phase III)	FDA approved in May 2019
Act on *SMN2* to increase SMN protein production	Antisense oligonucleotide that binds *SMN2* mRNA to modify splicing	Nusinersen	Intrathecal injection every 4 months	NCT01494701 and NCT01780246 (Phase I) NCT01839656 (Phase II) ENDEAR (Phase III) CHERISH (Phase III) NURTURE (Phase II) SHINE (Phase III)	FDA approved in December 2016
	Small molecule that alters splicing of *SMN2*	Risdiplam	Oral daily medication	FIREFISH (Phase II, III) SUNFISH (Phase II, III) JEWELFISH (Phase II) RAINBOWFISH (Phase II)	FDA approved in August 2020

3. Keinath M, Prior D, Prior T. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. The Application of Clinical Genetics. 2021;Volume 14:11-25.

Genetic Counseling and Education

Explaining condition and manifestation

History taking, pedigree

Explaining other testing modalities: electrodiagnostic studies, muscle biopsy

Offering genetic testing availability for diagnostic testing and family testing

Explaining supportive care with multidisciplinary collaboration

Routine follow up for patient

Conclusion

- Spinal muscular atrophy is a genetic autosomal recessive disorder
- Genetic testing as a gold standard examination for both patient and family determine family member status.

THANK YOU