CLINICAL QUIZ (p141) ANSWER

What is the diagnosis?

Clinical suspicion for spinal muscular atrophy (SMA) was raised in view of her severe hypotonia and muscle weakness. Multiplex Ligation-dependent Probe Amplification (MLPA) for gene dosage of survival motor neuron 1 (*SMN1*) gene and survival motor neuron 2 (*SMN2*) gene was performed. Homozygous deletion of exon 7 and exon 8 in *SMN1* gene with two copies of *SMN2* gene was detected in the patient (Figure 2A), confirming the diagnosis of spinal muscular atrophy. Parents are both heterozygous *SMN1* deletion carrier (Figure 2 B & C).

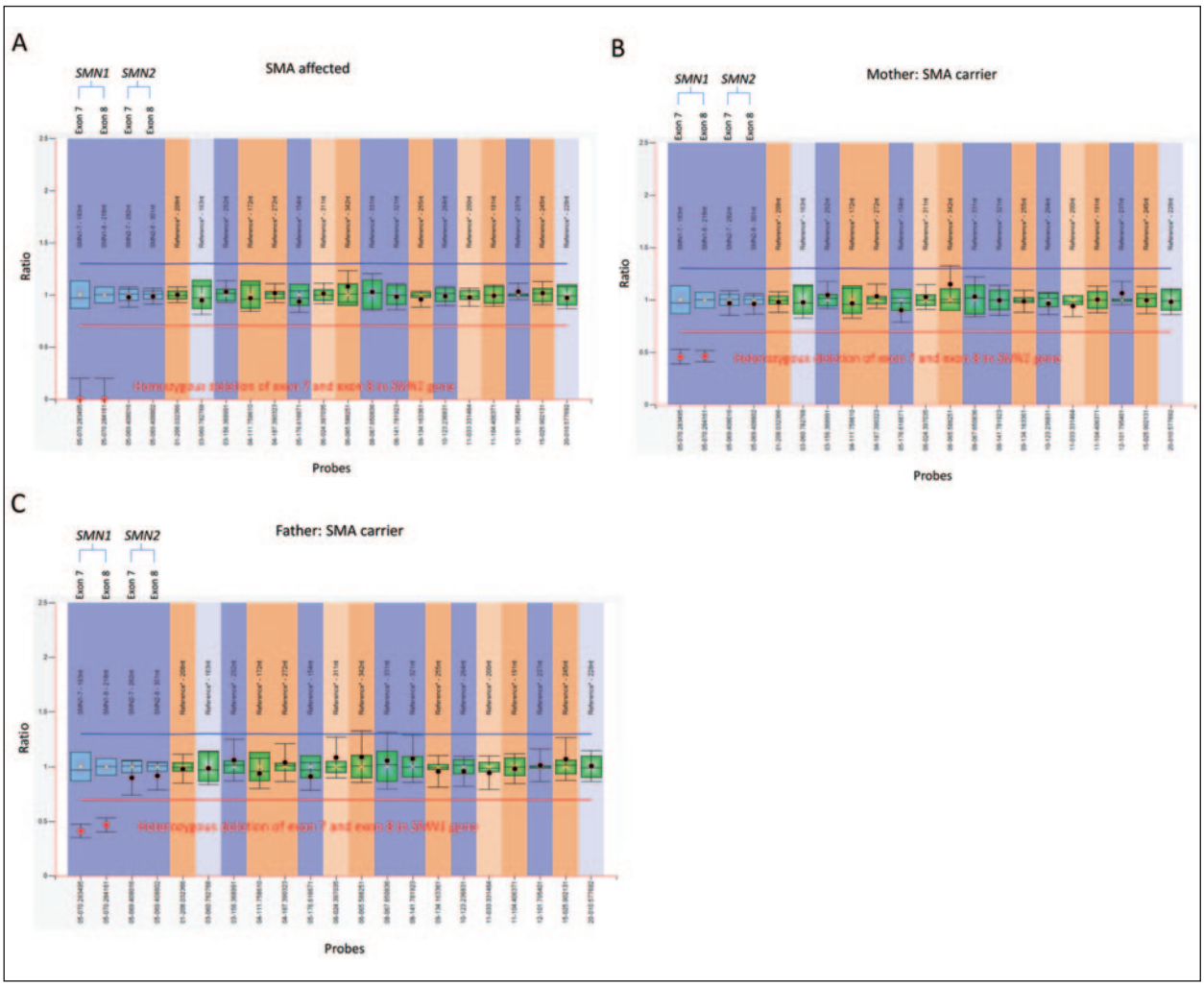

Figure 2 Multiplex Ligation-dependent Probe Amplification (MLPA) for gene dosage of survival motor neuron 1 (S*MN1*) gene and survival motor neuron 2 (*SMN2*) gene. (A) Result of the affected child showed homozygous deletion of exon 7 and exon 8 of *SMN1* gene (ratio= 0 for both exon 7 and exon 8 probes). There are 2 copies of exon 7 and exon 8 of *SMN2* gene (ratio ~1 for both exon 7 and exon 8). (B) & (C) Results of the mother and father showed heterozygous deletion of exon 7 and exon 8 of *SMN1* gene (ratio ~0.5 for both exon 7 and exon 8 probes).

What is the genetic anomaly associated with SMA?

Spinal muscular atrophy (SMA) is an autosomal recessive inherited neurological condition with a spectrum of clinical severity. It is caused by homozygous deletions or mutations in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13.2, resulting in deficiency of the SMN1 protein.[1,2] The SMN protein is critical to survival of neurons in the spinal cord, the absence of which results in enhanced neuronal death. The *SMN2* gene, often called the SMA "backup gene", produces some functional SMN protein which can partially compensate for the loss of SMN1 protein. Thus, its number plays a role in determining the clinical severity of the disease. The presence of three or more copies of SMN2 is associated with a milder phenotype. In our patient, only two copies of *SMN2* gene were detected.

What is SMA?

SMA is characterised by progressive hypotonia and muscular weakness due to degeneration of the anterior horn cells in the spinal cord. In some, the motor neurons of cranial nerves are also involved, but sensation and cognition are intact. Depending on the age of onset and clinical course, SMA is classified as type 0 to type 4, with type 0 (prenatal onset) and type 1 (infantile onset) being more severe and type 2-4 being less severe with later onset.[1] Our patient is likely to have SMA type 1 in view of genetic workup showing two copies of the *SMN2* gene, as well as infantile onset of symptoms.

Apart from symmetrical proximal muscle weakness, SMA patients face other physical challenges including progressive respiratory failure, feeding problem, joint contractures and scoliosis.[3] Those with milder types of SMA may be ambulatory initially but become wheelchair dependent with time. On the other hand, SMA type 1 patients may die from respiratory related complications by 2 years of age.

What is the treatment approach?

A team-based approach with multi-disciplinary care tailored for each family should be provided to SMA patients to optimise their quality of life. Apart from supportive care, intrathecal Nusineren, a novel disease modifying drug, was approved to treat SMA patients in 2016.[4] Nusineren is an antisense oligonucleotide that increases the expression of the survival motor neuron protein, thus resulting in improvement in motor function in SMA patients. In view of the high cost and uncertain long term effects, individualised treatment decision has to be made before commencement of such therapy.

References

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3. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin 2015;33:831-46.
4. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet 2016;388:3017-26.