PRENATAL DIAGNOSIS OF SPINAL MUSCULAR ATROPHY TYPE 0

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Types of SMA

• 5 subtypes based upon onset of symptoms and progression of weakness:
  – Type 0 – Most severe, prenatal onset by usually 30-36 weeks
  – Type 1 – Severe, Onset by 6 months and succumb by 1-2 years
  – Type 2 – Intermediate severity. Onset 6-18 months. Survive upto around 3 years
  – Type 3 – Mild, Onset anytime after 18 months. Normal lifespan
  – Type 4 – Adult onset with normal lifespan
Review of literature...

• Kirkinen et al (PND, 1994)- presented a case of SMA type 1 presenting antenatally with history of decreased fetal movements at 36 weeks but had reactive CTG and normal breathing movements. Target scan showed normal fetal activity.

• In 1999, Dubowitz – “Type 0 is an expanding clinical phenotype of Type 1 SMA”
• Nuchal edema, hydrops, body wall edema in second trimester may represent severe variant of SMA – Asha R et al (PND, 1997)

• Nuchal translucency increase in fetus with normal karyotype - Robert J. Stiller et (1999 PND)
Case history

• 30 yrs old Mrs. J who P2L1 came for pre-pregnancy counseling
• 3\textsuperscript{rd} degree consanguineous marriage
• 1\textsuperscript{st} child died ? Cause
• 2\textsuperscript{nd} child – floppy, hypotonia, feeding difficulty
• No significant anomalies noted in family pedigree
Obstetric history

- Gravida 1: Male baby born at term. 3.7 kg bw. Lethargic at 3 months, h/o recurrent respiratory infection. No h/o aspiration. Diagnosed as floppy infant -? Congenital myopathy ? SMA. Baby succumbed at 13 months ? Cause of death. No confirmatory tests done.
Obstetric history

Gravida 2:

• 1 yr old female child.
• Diagnosed as a case of spinal muscular atrophy
  – Born at term
  – Was normal upto 1 month.
  – Subsequently developed weakness
  – Recurrent aspiration requiring NG feeds.
• Mutation analysis of this child and mother were already done and referred for pre-pregnancy counseling to Mediscan.
Mutation analysis of proband showed deletion of exon 8 of SMN 1 gene.

Mutation analysis of mother showed that she is carrier of exon 8 deletion of SMN 1 gene.
Counseling

The couple was explained that

• SMA is an AR disorder with 25 % chance of recurrence.

• As mutation analysis was done for index child, prenatal diagnosis is possible in subsequent pregnancy.
The patient came for first trimester screening of next pregnancy...
USG at 13 - 14 wks

Decreased fetal activity
• CVS done to rule out chromosomal abnormality and SMA

Mutation analysis showed deletion of exon 8 of SMN 1 gene, similar to previous child
Spinal Muscular Atrophy

• Autosomal recessive
• Lower motor neuron disease causing muscle weakness and atrophy
• Causative gene : SMN (Survival Motor Neuron) gene
• Located on chromosome 5q
• Carrier frequency about 1:50 in general population
Structure of SMN Gene Region on 5q

mRNA Transcript

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Protein

- Δ7SMN: unstable
- f7SMN: stable
SMN1

• Multiple copies of SMN1 can be present
  – Normally (94.3%) - 2 copies
  – 2.1% - 3 copies
  – 0.7% - 4 copies
  – 2.9 % - 1 copy

• One copy of SMN is sufficient for normal functioning
SMN1

• Disease caused by:
  – Homologous deletion of SMN1 gene
  – Intragenic mutation in SMN1 gene when only one copy is present

• 2% of affected SMA individuals is due to *denovo* deletion/mutation wherein parents are not carriers
SMN2

• Deletion of SMN2 does not cause disease
• However it can act as a modifier – More copies of SMN2 gene can decrease severity
• Also sequence variants in SMN2 can modify severity. Eg .859G>C in exon 7 of SMN2 creates new exonic splicing enhancer (ESE)
Other genes

- Neuronal Apoptosis Inhibitory Protein (NAIP) gene
- P44 gene
- Their role in the disease is controversial
- Present close to SMN gene
- Many patients with SMN1 deletion have NAIP deleted also
- NAIP more often deleted in Type 1 than Type 2 and 3 – Hence increases disease severity
Molecular diagnosis

• PCR-RFLP
  – Detects homozygous exon 7 and exon 8 deletions

• Sequencing for point mutations

• Quantitative PCR
  – for carrier detection
PCR-RFLP

Exon 7

DraI restriction digestion

| 200 bp | ![](image) |
| 176 bp | ![](image) |
| 24 bp  | ![](image) |

SMN1

Normal/Carrier

Affected

Exon 8

Dde I restriction digestion

| 200 bp | ![](image) |
| 122 bp | ![](image) |
| 78 bp  | ![](image) |

SMN1

Normal/Carrier

Affected
SMA Type 0 clinical presentation

- Intrauterine onset
- Present with asphyxia or severe respiratory distress in the neonatal period
- Usually need immediate intubation and artificial ventilation
- Profound hypotonia and facial weakness
- Death within the first 3 months
SMA type 0 genetics

• Consistent homozygous deletion of exon 7 and 8 of SMN1

• A case report of 3 cases with SMA type 0 (Barzegar et al, 2010) – Additionally exon 5 of NAIP deleted
  – Further implicating this gene as a factor for disease severity

• However, none of these studies have reported prenatal diagnosis
Our case

3 consanguinous couple

Carrier for Exon 8 deletion

No mutation analysis done

Exon 8 deletion

Exon 8 deletion
• First case wherein prenatal diagnosis has confirmed SMA type 0 with exon 8 deletion with severe and early presentation

• SMN2 and NAIP exon 5 and exon 11 as modifiers are being looked into
Acknowledgements

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• Dr. Chandak of CCMB, Hyderabad for performing molecular testing in the index child, mother and fetus.
Thank you...