Peripheral Hypotonia And Areflexia In Infants: Think Beyond SMA

J Rohitha, Sayoni Roy Chowdhury, Suvasini Sharma, Leena Bharali, Richa Gupta, Priyanshu

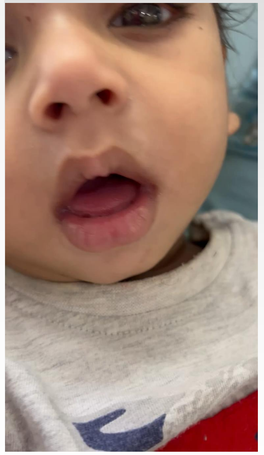
Division of Pediatric Neurology, Lady Hardinge Medical College

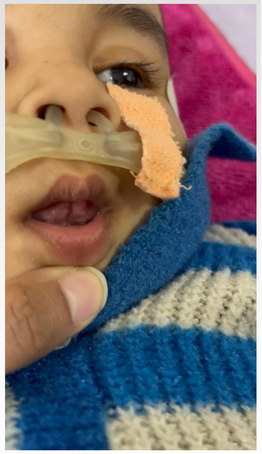
INTRODUCTION

- Spinal muscular atrophy (SMA) is the commonest cause of infantile onset peripheral hypotonia
- Clinically anterior horn cell involvement is characterized by proximal weakness, areflexia, muscle atrophy and tongue fasciculations
- Presence of additional UMN and systemic manifestations, alongside neuronopathy, categorizes these conditions into motor neuron disease plus syndromes

MATERIALS AND METHODS

- Retrospective review
- We describe four young male infants, aged 2-4 months who presented with SMA plus phenotype





CLINICAL PRESENTATION

	Case 1	Case 2	Case 3	Case 4
Age of symptom onset	Birth	Birth	Birth	4 months
Developmental delay	Motor	Global (motor > cognitive)	Motor	Global (motor > cognitive)
Paucity of limb movements	+	+	-	+
Recurrent LRTI	+	+	-	+
Family history	Second degree CM, history of 2 losses	Noncontributory	Noncontributory	Nonconsanguineous, history of 3 losses
a)LMN signs **Peripheral hypotonia, tongue fasciculations, areflexia**	+	+	+ (but no tongue fasciculations)	+
Bulbar palsy	-	+	+	+
b) UMN involvement	-	**Seizures**	-	-
c) Multisystemic features				
Dysmorphism	-	**+**	-	**+**
Organomegaly	-	**Hepatomegaly**	-	**Hepatosplenomegaly**
Others	**Failure to thrive , severe GER**	-	**Anaemia**	-
Total CPK	**1290 u/l**	Normal	Normal	Normal
NCV	-	-	Acute motor axonal polyneuropathy	-
SMN1 gene deletion	Negative	Negative	-	-
MRI brain	-	Sequalae to small bleeds in bilateral cerebral and cerebellar hemispheres	Normal	Abnormal T2 signal change in PV white matter, delayed myelination
Additional investigations	**3 mmol/L**	-	CSF study: Albumino-cytological dissociation	**Dyslipidemia**
WES	Likely pathogenic compound heterozygous variants in exon 5 (c.540del, p.Lys180AsnfsTer1) and and exon 3 (c.306T>G, p.Ile102Met) of RRM2B gene - AR	Likely pathogenic, homozygous variant in exon 20 (c.1732T>C p.Trp578Arg) in HSD17B4 gene - AR	Likely pathogenic, homozygous variant (Exon 2, c67+1G>A) in CD59 gene - AR	Pathogenic CNV - homozygous deletion on chr 4q24 – TBCK gene (exon 23)
Diagnosis	**Mitochondrial DNA depletion syndrome (MNGIE type)**	**D-bifunctional protein deficiency (peroxisomal disorder)**	**CD-59 associated immune mediated polyneuropathy with hemolytic anemia**	**A novel LSD – proposed as NCL - CLN 15**
Treatment	Supportive Care	Supportive Care	Immunotherapy	Supportive Care
Outcome	Expired during hospital stay	GDD, supportive care	Recovered completely with steroids	Supportive care, chronic respiratory issues

DISCUSSION

- Infantile onset motor neuronopathy can manifest as an isolated condition (SMA) or be a part of complex neurological disorder with systemic features.
- Additional neurological signs beyond anterior horn cell involvement, as seen in case 2 with seizures and extra-neurological features like severe GER with failure to thrive in case 1, dysmorphism and organomegaly in cases 2 & 4, and recurrent anemia requiring blood transfusions in infantile onset immune-mediated polyradiculopathy with poor response to intravenous immunoglobulin, prompted us to explore possibilities beyond common SMA mimics encountered in clinical practice.
- In the current era, genetic testing coupled with good clinical phenotyping bears immense diagnostic, therapeutic and prognostic implications.

RESULTS

- Complex large molecule disorder like lysosomal storage disorder, peroxisomal disorder and mitochondrial DNA depletion syndromes should be considered as differentials of SMA plus phenotypes.

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Contact : sharma.suvasini@gmail.com, rohitha128@gmail.com.