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Sids: The Search For Genetic Etiology

Dr. Deepak.K[1], Dr. Dasaratha Ramaiah [2]
[1] *NICU Fellow, Department of Neonatology, Rural Development Trust Hospital, Bathalapalli, Andhra Pradesh, INDIA*
[2] *Professor, Department of Neonatology, Rural Development Trust Hospital, Bathalapalli, Andhra Pradesh, INDIA*

Abstract:
Background*: Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant less than one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history [1]. The rate of SIDS peaks between two and four months of age, and 90 percent of cases occur before six months of age. Approximately 12 percent of sudden unexpected infant deaths (SUIDs) occur during the neonatal period and 4 percent during the first week of life.[2]*
Case*: Second order female baby born to consanguineous parents, through normal vaginal delivery, cried immediately after birth, Inj. Vitamin K given at birth, started on breastfeeding and shifted to mother side. At 33hrs of life baby appeared cyanosed & was unresponsive to tactile stimulus, heart sounds were not audible & there were no central or peripheral pulses. Resuscitation done according to NRP but could not revived, hence baby declared death.*
Conclusion: *One genetic factor contributing to infant postnatal SIDS is PDE (Pyridoxine Dependent Epilepsy)*
Key Word*: SIDS, Sudden Infant Death Syndrome, Gene, SUIDS, Genetic, Review*

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I. Introduction

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant less than one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history [1].

The rate of SIDS peaks between two and four months of age, and 90 percent of cases occur before six months of age. Approximately 12 percent of sudden unexpected infant deaths (SUIDs) occur during the neonatal period and 4 percent during the first week of life.[2]

The mechanism of sudden death is unknown. The most compelling hypothesis involves a brainstem abnormality or maturational delay related to neuro regulation or cardiorespiratory control, combined with a trigger event such as airflow obstruction. The mechanism most likely involves abnormalities of serotonin (5-hydroxytryptamine [5-HT]) signaling [3].

According to the consensus definition from the 3rd International Congress on Sudden Infant and Child Death. SIDS occurs in approximately 1/1000 live-born infants and is the leading cause of post-neonatal mortality in developed countries. There are several well-described extrinsic and intrinsic risk factors that raise the risk of SIDS, such as male sex, prematurity, maternal alcohol or tobacco exposure, prone sleep position and sleeping on soft bedding or on a shared sleep surface.

The leading etiological model of SIDS is the "triple risk" model which postulates that SIDS occurs in a biologically vulnerable infant during a critical developmental period, when triggered by a stressor. Intrinsic factors leading to biological vulnerabilities, including genetic factors, could lead an infant to be susceptible to certain conditions that would otherwise not be lethal, such as illness, fever, or environmental factors such as sleep position or ambient temperature [4].

Indeed, several lines of evidence suggest that SIDS has genetic underpinnings, including a 4- to 5-fold relative risk of SIDS in subsequent siblings and an increased SIDS risk in monozygotic twins compared to dizygotic. Understanding the genetic factors predisposing some infants to SIDS is a substantially difficult task

In most disciplines of medicine, a biological condition is first discovered and thoroughly described prior to a genetic cause being successfully identified. However, in SIDS genetic research this has occurred in reverse: genetic testing and research has helped elucidate plausible mechanisms of death in SIDS. SIDS is understood as a heterogeneous condition, and we only have a crude understanding of what conditions contribute to the mechanisms responsible for its fatal outcome.

II. CASE REPORT

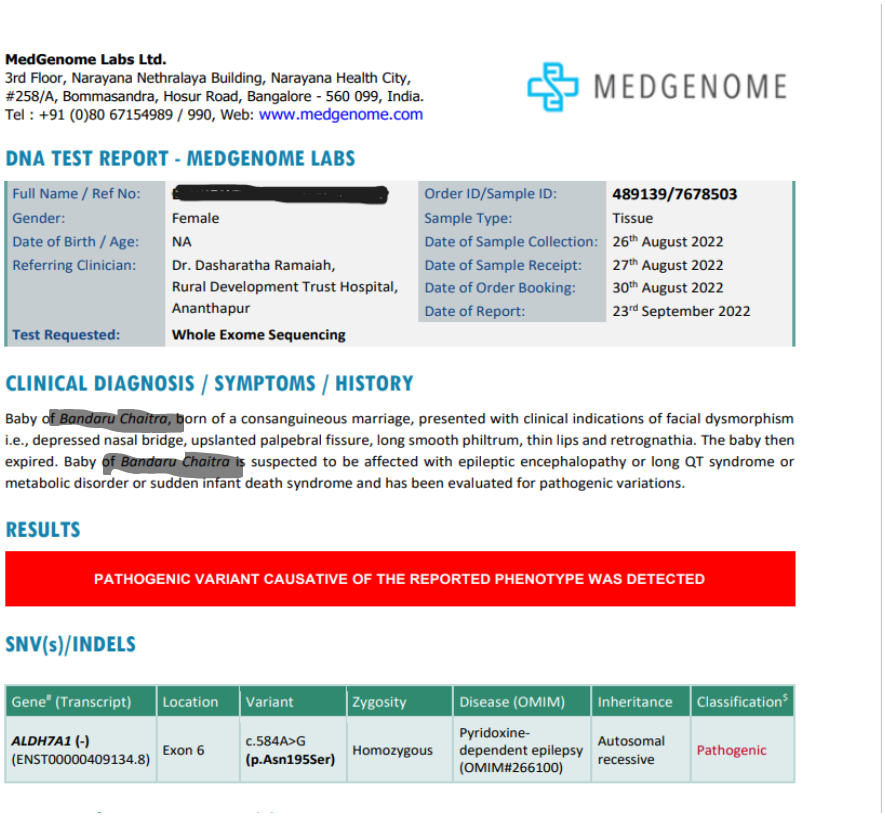
Second order female baby born to consanguineous parents, through normal vaginal delivery, cried immediately after birth, Inj. Vitamin K given at birth, started on breastfeeding and shifted to mother side. At 33hrs of life baby appeared cyanosed & was unresponsive to tactile stimulus, heart sounds were not audible & there were no central or peripheral pulses. Resuscitation done according to NRP but could not revived, hence baby declared death.

On post-mortem examination we could find certain dysmorphic features like depressed nasal bridge, thin upper lip, up slanting palpebral fissure, long smooth philtrum, retrognathia. Additionally, baby born to consanguineous couple who had bad obstetric history, they had one abortion at gestational age and one term baby expired on D1 of life I/V/O severe respiratory distress

On reviewing medical records baby had jerky limb movements @ 9 hrs of life which was reassured as jitteriness, serum calcium sent which was normal, retrospectively we suspected those jerky movements as form of seizures, with this examination and history findings we suspected genetic pathology and counselled parents for postmortem genetic study

Tissue Sample was taken from pulp of left thumb, keeping the following clinical suspects

A) Genetic Epileptic Encephalopathy
B) Long QT Syndrome
C) Metabolic Disorder
D) Sudden Infant Death Syndrome



MedGenome Labs Ltd.
3rd Floor, Narayana Nethralaya Building, Narayana Health City,
#258/A, Bommasandra, Hosur Road, Bangalore - 560 099, India.
Tel : +91 (0)80 67154989 / 990, Web: www.medgenome.com

MEDGENOME

DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	[redacted]	Order ID/Sample ID:	**489139/7678503**
Gender:	Female	Sample Type:	Tissue
Date of Birth / Age:	NA	Date of Sample Collection:	26th August 2022
Referring Clinician:	Dr. Dasharatha Ramaiah, Rural Development Trust Hospital, Ananthapur	Date of Sample Receipt:	27th August 2022
		Date of Order Booking:	30th August 2022
		Date of Report:	23rd September 2022
Test Requested:	**Whole Exome Sequencing**		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Baby of *Bandaru Chaitra*, born of a consanguineous marriage, presented with clinical indications of facial dysmorphism i.e., depressed nasal bridge, upslanted palpebral fissure, long smooth philtrum, thin lips and retrognathia. The baby then expired. Baby of *Bandaru Chaitra* is suspected to be affected with epileptic encephalopathy or long QT syndrome or metabolic disorder or sudden infant death syndrome and has been evaluated for pathogenic variations.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
ALDH7A1 **(-)** (ENST00000409134.8)	Exon 6	c.584A>G **(p.Asn195Ser)**	Homozygous	Pyridoxine-dependent epilepsy (OMIM#266100)	Autosomal recessive	Pathogenic

III. DISCUSSION

By definition, SIDS, as the unexplained death of a seemingly healthy baby less than a year old, is an undiagnosed "disease". As such, it can be approached similarly to other undiagnosed diseases. In clinical medicine, if a living individual presents with an unknown or unexplained disease, the standard practice is to exhaustively investigate until the cause is (hopefully) understood. This process often includes conducting genetic studies.

Siblings of SIDS victims have a five- to sixfold increase in risk for SIDS. The small but increased risk of SIDS in siblings of SIDS victims is probably due to a combination of biologic and/or epidemiologic factors. In this case first child also had history SIDS after birth, but genetic evaluation not done. After genetic evaluation by Whole Exome Sequencing baby diagnosed with PDE (Pyridoxine Dependent Epilepsy)-Pathogenic Variant-Autosomal Recessive Inheritance

Pyridoxine Dependent Epilepsy (PDE) also known as Pyridoxine-dependent (ALDH7A1) developmental and epileptic encephalopathy (PD-DEE). It is classified under Developmental and epileptic encephalopathies (DEEs) [5].

Developmental and epileptic encephalopathies (DEEs) are severe syndromes associated with refractory seizures and abnormal neurodevelopmental outcomes, which are related to both the underlying syndrome etiology and the seizures or epileptiform abnormalities [6].

DEEs classified into
1) Early infantile DEE
2) KCNQ2-DEE
3) PD-DEE and P5PD-DEE

Pyridoxine Dependent Epilepsy: — Pyridoxine-dependent (ALDH7A1) developmental and epileptic encephalopathy (PD-DEE) and the related disorder, pyridoxamine 5'-phosphate oxidase deficiency (PNPO) developmental and epileptic encephalopathy (P5PD-DEE), are rare but treatable genetic causes of medically refractory neonatal epilepsy. Both syndromes lead to metabolic defects within the lysine degradation pathway.

ETIOLOGY:
- These are disorders that result in a cofactor or vitamin deficiency are important to recognize because they represent rare but treatable metabolic causes of refractory neonatal seizures.

- Most cases of PDE are due to alpha-aminoadipic semialdehyde (alpha-AASA) dehydrogenase (also known as antiquitin, or ATQ) deficiency, an autosomal recessive inborn error of metabolism caused by defects in the ALDH7A1 gene that lead to accumulation of alpha-AASA and pipecolic acid in plasma, urine and CSF [7]

CLINICAL FEATURES:

- Most patients with PD-DEE or P5PD-DEE develop seizures in-utero or shortly after birth and have co-occurring encephalopathy. However, a later presentation, typically in the first three years of life, is seen in up to one-quarter of patients, with rare patients presenting in adolescence [8].
- Antiquitin deficiency and PNPO deficiency have overlapping phenotypes. Most patients present with seizures in the neonatal period that can be focal, generalized, tonic, or myoclonic; some patients have infantile spasms 8. Seizures may be frequent and evolve to status epilepticus.
- Up to half of children with PNPO deficiency are born at ≤37 weeks gestation [8].

Evaluation and diagnosis:

- The interictal EEG is typically markedly abnormal prior to treatment with a burst-suppression pattern and abundant multifocal epileptiform discharges. Brain MRI may be normal or show white matter oedema in the setting of severe encephalopathy [9].
- MRI abnormalities include ventricular enlargement and corpus callosum hypoplasia.
- Metabolic testing should not delay treatment, but biochemical evaluation with measurement of urine and plasma alpha aminoadipic semialdehyde (alpha-AASA) and/or plasma pipecolic acid can aid the diagnosis.

Genetic testing is useful to detect pathogenic variants in the ALDH7A1 or PLPB genes in PD-DEE, or the PNPO gene in P5PD-DEE.

Treatment:

- Pyridoxine-dependent epilepsy (PDE) due to antiquitin (ATQ) deficiency and the related disorder, pyridoxamine 5'-phosphate oxidase (PNPO) deficiency, are rare but treatable genetic causes of medically refractory neonatal seizures [9].
- Sequential therapeutic trials of pyridoxine (100 mg IV injections, repeated every 5 to 15 minutes up to a maximum of 500 mg with continuous electroencephalography (EEG) monitoring, or 15 to 30 mg/kg per day orally in three divided doses) and pyridoxal 5'-phosphate (PLP, the active form of pyridoxine [vitamin B6]) should be given to neonates with seizures unresponsive to conventional antiseizure medications, particularly if the cause of the seizures is not known [10].
- Trials of IV pyridoxine should be performed with EEG and close cardiopulmonary monitoring, as there is a risk of apnea with pyridoxine, particularly when given IV. If there is no response to pyridoxine or PLP, leucovorin (2.5 mg IV) may be administered, since some cases of antiquitin deficiency respond better to leucovorin (folinic acid) than pyridoxine [11].
- Patients with antiquitin deficiency should receive chronic supplementation with pyridoxine and/or leucovorin and may also benefit from a lysine-restricted diet supplemented with lysine-free amino acid formula [11].
- Long-term treatment doses of pyridoxine vary between 15 and 30 mg/kg/day for infants [12].
- Some commercially available lysine-free formulas are also free of tryptophan, in which case tryptophan should be supplemented.
- Long-term treatment with high doses of pyridoxine can result in peripheral neuropathy. Infants with PNPO deficiency should receive chronic oral PLP supplementation [13].
- Patients can have a normal neurodevelopmental outcome with early, appropriate treatment, but many will experience neurodevelopmental delays.

IV. Conclusion

One genetic factor contributing to infant postnatal SIDS is PDE (Pyridoxine Dependent Epilepsy).

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