ISSN: 0975-3583,0976-2833 VOL15, ISSUE 08, 2024

Recurrent Neu-Laxova syndrome in subsequent pregnancies: a case report and implications for genetic counselling

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ABSTRACT:

Neu-Laxova syndrome (NLS) is a rare and lethal disorder with numerous congenital anomalies. This rare disorder is characterised by heterogeneous neurodevelopmental defects, which involves various systems starting from the CNS, musculoskeletal, skin, limb defects etc. we present the case of a patient whose first pregnancy was a congenitally malformed fetus suspected with Neu-Laxova syndrome during her second trimester ultrasound. The ultrasound diagnosis was confirmed with a genetic study of the amniotic fluid. The results showed a variant of PHGDH gene mutatuon in apparent homozygosis associated with NLS-1 syndrome of autosomal recessive inheritance. The couple presented to us with second pregnancy and the present fetus showed recurrences of the previous outcome on ultrasound. Here we are presenting the detailed sonographic, clinical and genetic examination of the above cases with the discussion.

INTRODUCTION:

Neu-Laxova syndrome is a rare multisystem disorder most commonly inherited by autosomal recessive inheritance. This condition is associated with grave malformations involving the derivatives of the neuroectoderm in the foetuses.[1] This condition complex was initially observed after delivery of the babies. Later with the available prenatal diagnostic tools like ultrasound which is now widely available is helping in making a probable diagnosis of Neu-Laxova syndrome in the antenatal period. The main features observed in affected foetuses are microcephaly, somatic malformations like short broad neck, limb anomalies and dermatological malformations like peripheral edema, ichthyosis and facial dysmorphism. All

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the above features clubbed together the syndrome can be summarized as a “neuro-ectodermal dysplasia”.

According to the literatures most of the affected children either die in utero or still born or die due to respiratory failure or infections in the neonatal period. Less than 90 cases have been described in the literatures with varying clinical expressions and genetic mapping so far. NLS represents a severe variant of the serine metabolism disorders. NLS manifests as a wide spectrum phenotype. This varying phenotypic expression of the NLS makes the diagnosis challenging with ultrasond, while genetic analysis are used in arriving at a definitive diagnosis of NLS. Hence our case report also describes clinical syndrome of NLS with the discussion.

CASE REPORT:

A 20 years old primigravida with 3rd degree consanguinity, conceived naturally with normal first trimester ultrasound and showed low risk for trisomy on first trimester combined screening. She has no significant personal or family history of interest. Blood investigations during first and second trimester were unremarkable. Second trimester targeted ultrasound examination was done which showed fetal biometry below the 5th percentile for that period of gestation, a diagnosis of early IUGR was made. The ultrasound also revealed oligohydramnios with restricted fetal movements. A detailed fetal morphological study was performed, which showed some major morphological abnormalities in the foetus.

The detailed ultrasound examination revealed following abnormalities at the intracranial level: microcephaly, loss of cortical volume with abnormal cortical maturation, dysgenetic corpus callosum, hypoplastic cerebellum and verminan hypoplasia. Along with the above CNS findings the fetus showed facial dysmorphisms, thickened skin, ectropion of the lids and eclabium. The fetal limbs showed abnormal posturing of both the upper and lower limbs, bilateral rocker bottom foot (figure-1) and neuro arthogyropsis. The above ultra-sonographic findings were in consistent with the Neu-Laxova syndrome which required further genetic analysis to confirm the diagnosis.

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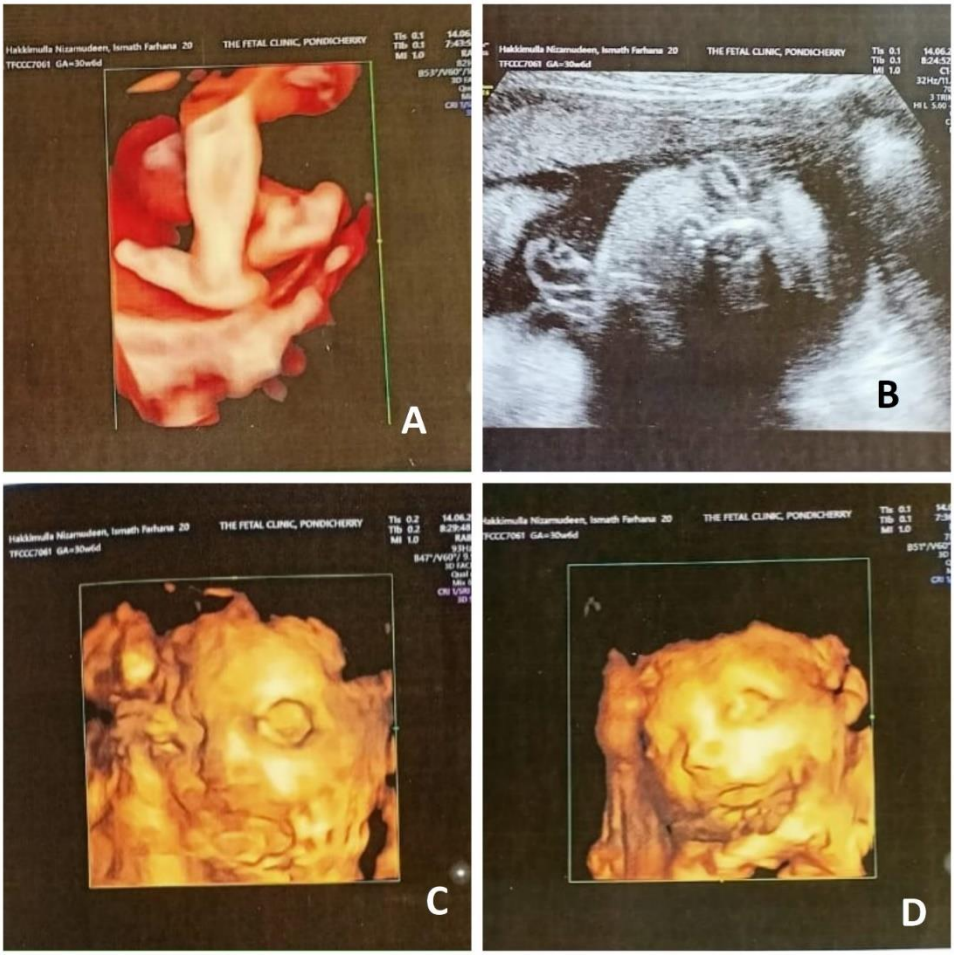

Figure-1: Ultrasound image showing A-Rocker bottom foot, B-Ectropion of eyelids, C-Fish mouth appearance, D-Micrognathia

She was offered amniocentesis at 22 weeks, that would help arriving at a definitive diagnosis. With the reports awaited her pregnancy continued and the women went into spontaneous labour and delivered a stillborn female baby with external features of microcephaly, micrognathia, slanting forehead, hypertelorism, flat nose and flat nasal bridge (figure-2), diffuse subcutaneous edema, lamellar ichthyosis, rocker bottom foot and clenched hands (figure-3).

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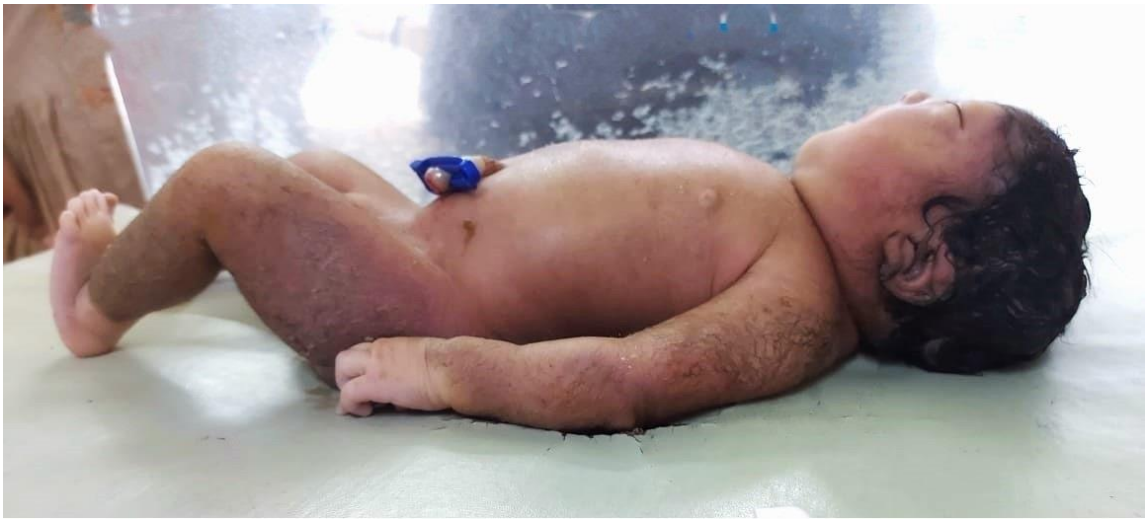

Figure-2: Image of stillborn fetus showing features of slanting forehead, micrognathia, flat nose and flat nasal bridge

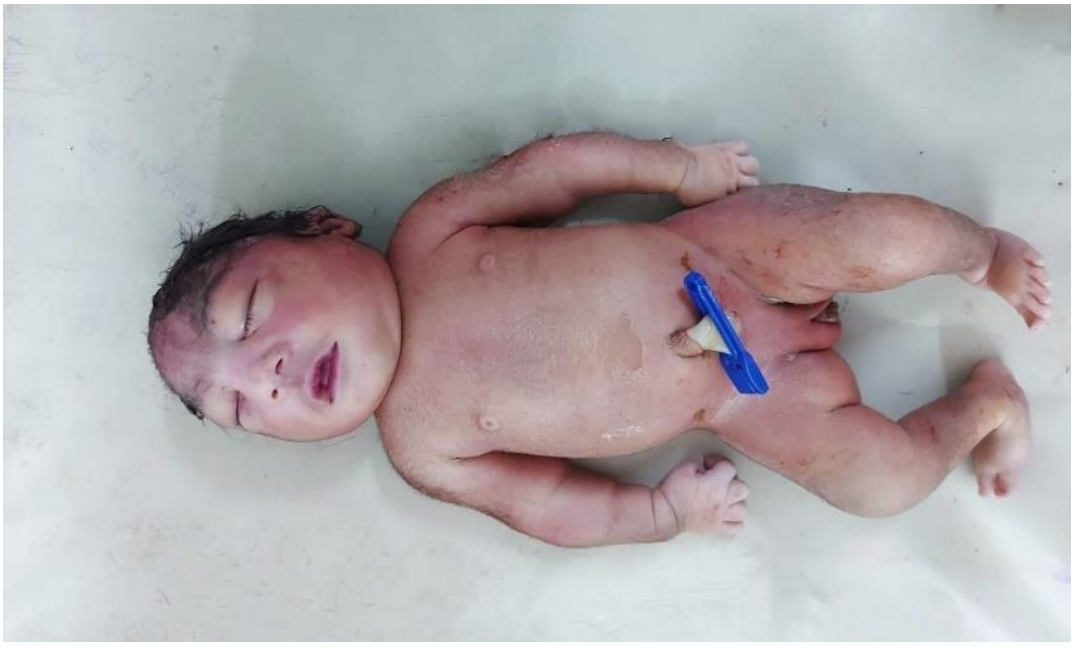

Figure-3: Image of stillborn fetus showing diffuse subcutaneous edema, lamellar ichthyosis, rocker bottom foot and clenched hands

An extended genetic study of the amniotic fluid revealed a pathogenic variant of uncertain significance consistent with the phenotype. This variant was identified in apparent

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homozygosis in the PHGDH gene, associated with NLS-1 syndrome by autosomal recessive inheritance. PHGDH gene of intron 5 with variant c511-5A>G and genome chr1g.120277252A>G with homozygosity was studied consistent with Neu Laxova syndrome-1. This variant c511-5A>G has allele frequency of 0.0004% in the gnomAD and novel in 1000 genome database. For these reasons, this variant has been classified as Uncertain Significance and reported to the ClinVar database.

The couple had no similar instances in their extended family. After one year she become pregnant again, present pregnancy had a normal first trimester ultrasound as well as a low-risk first-trimester screening for trisomy. The second trimester targeted ultrasound unveiled a small of gestational age fetus with the recurrence of previous outcome. CNS features of microcephaly, absent cavum septum pellucidum, dysgenetic corpus callosum, loss of cortical volume with absent cortical maturation and hypoplastic cerebellum. Facial dysmorphism like frontal sloping of forehead, relative proptosis and mild retrognathia. Abnormal posturing of lower limbs was present. The couple along with the help of the Obstetrics team, opted for medical termination of pregnancy at 21 weeks. The fetus showed features of generalised edema, proptosis of the eyes, retrognathia, and lower limb digital abnormalities (figure-4, 5) on external examination.

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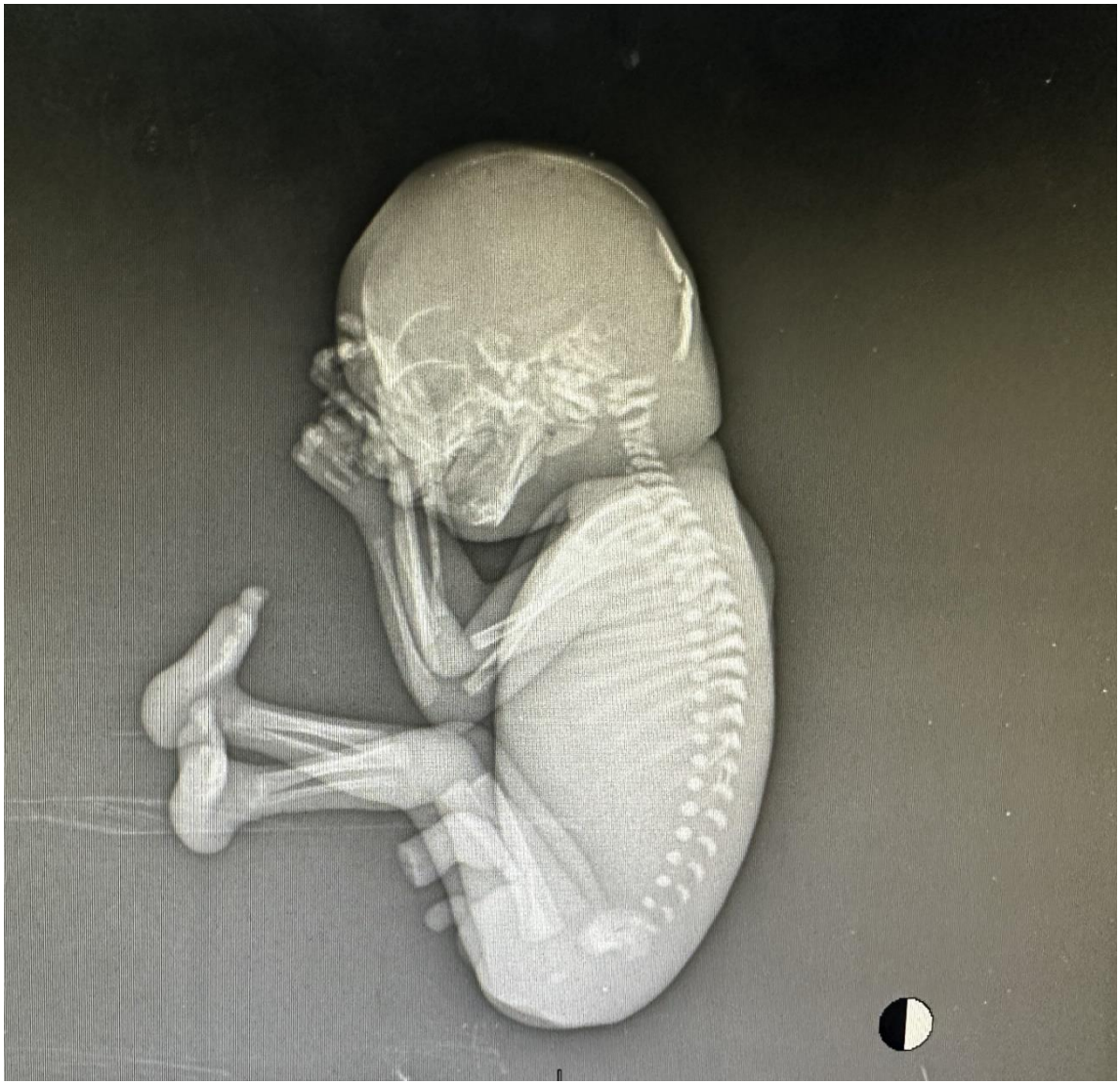

Figure-4: X-ray image of the fetus showing diffuse edema, retrognathia, rocker bottom foot

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Figure-5: Image of fetus showing generalised edema, proptosis of the eyes and lower limb digital abnormalities

DISCUSSION:

Neu et al.[1] in 1971 studied three sibling with microcephaly and multiple congenital anomalies, an year after this Laxova et al.[2] studied similar multisystem congenital anomalies running in family and proposed this condition as autosomal recessive condition. Later Lazjuk for the first time used a new term "Neu-Laxova syndrome" for this multisystem disorder in 1979.[3] until recently, the etiopathogenesis of this syndrome was identified by genetic analysis of the affected individuals and fetuses. In the year 1996 Jaeken et al in their study measured the cerebrospinal fluid levels of serine in two brothers with microcephaly, epilepsy, hypertonia etc., they found decreased 3-phosphoglycerate dehydrogenase in them. This PHGDH is involved in serine biosynthesis.[4] In 2014, Ranad Shaheen et al. conducted a gene mapping study among three NLS affected families and found homozygous mutation in PHGDH gene and serine deficiency among affected individuals in the families.[5] This disorder is included in

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Mendelian Inheritance in Man, a catalog of human gene and genetic disorders (NLS [MIM 256520]). They also proposed that NLS could be due to severe deficiency of PHGDH gene and named this entity as Neu-Laxova syndrome type 1 (NLS-1).[5]

Later that year Acuña-Hidalgo et al identified two genes associated in the de-novo synthesis of L-serine, phosphoserine aminotransferase 1 (PSAT1) and phosphoserine phosphatase (PSPH). NLS caused by mutation in the later genes explained by Acuña-Hidalgo et al was classified as Neu-Laxova syndrome type 2 (NLS-2) with similar phenotypic expression as NLS-1.[6]

Serine is essential for the synthesis of brain lipids namely sphingolipids and gangliosides which are vital for the normal neuronal transmission. Above mentioned genes involved in the de-novo synthesis of serine are PHGDH, PSAT1, and PSPH genes. The mutations of the above genes can be seen in both consanguineous and non-consanguineous relationships. NLS is frequently suggested to be inherited in an autosomal recessive manner in many conditions. The clinical spectrum of serine deficiency disorders are broad, ranging from mild cases of epilepsy and developmental delay to severe cases of Neu-Laxova syndrome.

The fundamental characteristics of NLS are abnormalities in somatic growth, brain, and skin development, as well as numerous additional anomalies that may indicate a malformation sequence or primary malformations. Growth restriction is typically detected during the second trimester ultrasonography.

The diagnostic features are,

- **Intrauterine growth retardation** (87%)
- **Cutaneous manifestation:** Generalised edema (73%), icthyosis
- **CNS malformations:** microcephaly (85%), hypoplastic cerebellum (36%), lissencephaly (45%), hypoplasia/agenesis of corpus callosum (36%)
- **Craniofacial dysmorphism:** receding forehead (81%), proptosis (56%), a flattened nose (79%), micrognathia (69%), hypertelorism (49%), deformed and low set ears.
- **Limb anomalies:** hypoplasia or syndactyly of fingers and toes (48%) and flexion deformities / arthogyropsis (80%). [6]

Scott C I et al [7] proposed in 1981 in view of the severity of CNS system involvement in neu-laxova syndrome and associated skeletal manifestation such as contractures and syndactyly

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could be initiated by the malformation of brain in-utero, this have been labelled together as Cerebroarthrodigital (CAD) sequence. Contractures are common in NLS and occasionally accompanied by the formation of skin contractures (pterygium). These contractures are linked to hypoplasia of the skeletal muscles beneath.[8] Apart from the CAD sequence explanation mentioned before, there is also a proposal suggesting that NLS could be an innate error in fat metabolism. The latter was brought about by the widely publicised finding of a notable build-up of fat and myxoedematous material in the dermis over the entire body; this accumulation contributes to the characteristically edematous appearance of affected foetuses, who are occasionally referred to as "hydropic.".[9] Subcutaneous edema is a common, variable-intensity symptom that is most noticeable in the extremities, giving appearance as "inflated gloves." In its most severe form, it can be recognised as generalised hydrops fetalis. Skin could be typically ichthyotic with noticeable hyperkeratosis. This can mimic the appearance of other ichthyotic illnesses and colloidon membranes disease.

A focused ultrasound performed in the second trimester may reveal:

- Polyhydramnios (30%)
- Intrauterine growth retardation (87%)
- Hypoechoic skeletal structures
- Microcephaly, ocular proptosis, retrognathia,
- Restricted movement with flexion abnormalities

The differential diagnosis of NLS arises prenatally in foetuses with restricted mobility and CNS malformations. This includes cerebro-ocular-facial-skeletal (COFS) syndrome, Walker-Warburg syndrome, Pena-Shokeir syndrome type-I, cerebro-arthrodigital syndrome, Smith-Lemli-Optiz syndrome and Miller-Dieker syndrome.[10]

Along with serial prenatal ultrasound, genetic counselling is recommended to high-risk families with history of consanguineous marriage and history of stillborn babies with features akin to Neu-Laxova syndrome. Further genetic testing abets the previous knowledge of the mode of inheritance. Genetic testing is expedient in genetic counselling, due to the varying phenotypic spectrum of the disorder. Overall, the prognosis of NLS is poor. Prognostic ranges have expanded, nevertheless, because of the disorder's diverse phenotypic spectrum. Serine supplementation of the affected embryos in utero and immediately after birth appears to be an attractive treatment of NLS, it is found to reduce the severity of developmental deficits in those

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neonates who survived with milder form of serine deficiency disorders.[11] Establishing a molecular diagnosis of the disease at the stage of embryonic development is a challenge to this therapeutic approach. Mainly because of the lack of availability of molecular diagnostic tests in remote places and it's high cost.

CONCLUSION:

To make a diagnosis of Neu-Laxova syndrome the collaboration of prenatal diagnostic services and genetics are indispensable. The public and high risk families should have awareness of genetic counselling and the risks associated with consanguinity in developing this disorder. Hence preconceptional genetic counselling for the affected families is emphasized to reduce the incidence of NLS. Prenatal imaging studies with ultrasound has been very effective in arriving at this diagnosis offering the couple early decision for termination of pregnancy with severe phenotypic deformities and less compatible with life foetuses. One promising therapy strategy for lowering the severity of the condition in the future seems to be supplementing affected embryos with serine. However, more research is needed to confirm the efficacy and safety of serine supplementation both during pregnancy and after delivery.

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