

# New Insights on Genetic Features of Neu-Laxova Syndrome

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## ABSTRACT

**Background:** This study aimed to present a rare case of Neu-Laxova syndrome (NLS) and review the newly revealed genetic features of the disease in hopes to find a way for early interventions.

**Case report:** Female newborn with NLS was born at 30 weeks of gestation to consanguineous parents. The last prenatal ultrasound imaging revealed severe intrauterine growth restriction and microcephaly without polyhydramnios. The newborn had significant dysmorphic features, such as microcephaly, slanted forehead, protruding eye, flattened nose, micrognathia, cleft palate, ichthyosis skin, edematous hands and feet and flexion contractures of the joints. Moreover, she had the usual female karyotype. Results of plain x-ray imaging demonstrated microcephaly, kyphosis, and arthrogyposis.

**Conclusion:** According to the results of this study, NLS is a severe serine deficiency disorder. Given the confirmation of the possibility of diagnosing NLS early in gestation by several studies, it is suggested that early maternal supplementation with serine and glycine be used in families at risk of this disease or those who are diagnosed in early gestation with NLS in order to decrease the severity and fatality of the disease.

**Keywords:** Deficiency, Microcephaly, Serine

## Introduction

Neu-Laxova syndrome (NLS) is a lethal congenital anomaly with a constellation of distinct clinical features, which involve the central nervous system, skin, face, and limbs. Involvement of skeletal, genitourinary, pulmonary, cardiac and gastrointestinal systems have also been reported in previous studies (1). Almost 89 cases of NLS have been reported, and recent studies have revealed some of the genetic features of this syndrome (2, 3). In this article, a female newborn is presented with NLS from consanguineous parents without prior history of any genetic abnormalities. This is the second case in our country.

## Case report

A 35-year-old woman (gravida 4, para 3, living child 0) was admitted in our hospital at 30 weeks of gestation due to uterine contractions. She gave birth to a female newborn with multiple congenital anomalies and a terrible facial appearance through a normal vaginal delivery.

The newborn was dead soon after delivery. Parents were first cousins and had three healthy sons with no medical or genetic diseases. The mother had no history of infection, smoking, alcohol or substance abuse during pregnancy. Her prior antenatal measurements were not available, with the exception of the last ultrasound imaging, which was performed two weeks before delivery, revealing severe intrauterine growth restriction (IUGR) and microcephaly. In addition, no polyhydramnios was observed.

The newborn had significant dysmorphic features; severe microcephaly, slanted forehead, hypertelorism, protruding eye, absent eyelids, flattened nose, thick lips, micrognathia, large cleft palate, short neck, low-set ears and yellow, ichthyotic skin. Her hands and feet were severely edematous. Syndactyly was noted in the fingers and toes. Flexion contractures of the joints were observed due to the restricted skin. External female genitalia with restricted skin and no labia

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major were also observed (Figure 1). Cytogenetic examination demonstrated a normal female karyotype. Moreover, plain x-ray imaging was performed, revealing microcephaly, kyphosis, and arthrogryposis. Given the rejection of autopsy request by the parents, we were unable to assess any further possible gastrointestinal, lungs, liver and skin abnormalities. Parents gave a written informed consent for publishing this case report.



**Figure 1.** A 30-week-old newborn female, presented with NLS having microcephaly, slanted forehead, protruding eye, absent eyelids, flattened nose, micrognathia, low-set ears, ichthyotic skin, edematous hands and feet, and flexion contractures of the joints

## Discussion

Consanguineous marriages are very common in the Middle East; therefore, 33% of the reported cases were from this region. Parental consanguinity was present in 48% of the reported cases (1-3). Since the first reports in early 1970s, it was suggested that the condition is inherited in an autosomal recessive way with 25% recurrence risk (4).

Recently, the etiology of this syndrome was revealed at the gene levels, indicating mutations in

three important genes, which are responsible for serine biosynthesis pathway (2, 3). In this regard, Shaheen et al. (2014) reported mutations in phosphoglycerate dehydrogenase (PHGDH) in three affected individuals with consanguineous parents (2). Generally, this gene encodes the first enzyme in the pathway of de novo serine synthesis. PHGDH mutation was first reported in 1996 in two brothers born to consanguineous parents, who had congenital microcephaly, epilepsy, growth retardation, psychomotor retardation, hypertonia and hypogonadism (5).

In a study conducted by Acuna-Hidalgo et al., mutation was observed in two other genes; firstly, the PSAT1 gene, which encodes phosphoserine aminotransferase, the enzyme for the second step in the serine biosynthesis; and secondly, the PSPH gene, which encodes phosphoserine phosphatase, which catalyzes the last step of serine biosynthesis (3). The first case of PSAT1 deficiency was found in 2007 in two British siblings with microcephaly, hypertonia, intractable seizures and psychomotor retardation. The Cranial imaging of the first patient, who died at seven months, revealed generalized brain atrophy, hypoplasia of cerebellum and poor development of white matter. On the other hand, the second sibling was treated with serine and glycine since birth and had a normal outcome at three years (6). PSPH deficiency was first identified in 1997 in a Belgian boy with facial dysmorphism, IUGR, microcephaly and psychomotor retardation. Patient was treated with oral serine, resulting in a slight catch up of head growth following the treatment (7). Recently, Vincent et al. reported about a multiplex consanguineous Pakistani family with three affected individuals with PSPH gene mutations, who exhibited intellectual disability, hypertonia, congenital microcephaly and seizures [8]. It seems that mutation in the PSPH gene accounts for milder forms of the disease; the final phosphatase step in serine biosynthesis pathway could be bypassed to some extent and even low levels of dephosphorylation of O-phosphoserine could be observed without this enzyme (3).

There are many similar clinical features observed in three reported cases with milder phenotypes of NLS, who lived more than six months (1, 9), and the reported cases of PHGDH, PSAT1, and PSPH deficiencies (5-7). These findings indicated that NLS, PHGDH, PSAT1, and PSPH deficiencies were all part of a spectrum, caused by a defective serine synthesis pathway. Moreover, NLS was recognized at the severe end of this spectrum (2, 3).

## Conclusion

According to the results of the current research, which revealed that NLS is a severe serine deficiency disorder (2, 3), and due to the documentation of the possibility of diagnosing NLS early in gestation by many studies (10), and given the many reports on multiple affected siblings in some families (4, 9), it is suggested that early maternal supplementation with serine and glycine be used in families at risk of the studied condition or those who are diagnosed with this disease in early gestation age so that the severity and fatality of the disease be decreased. This is based on the fact that cases with similar genetic features of PHGDH, PSAT1, and PSPH deficiencies have shown significant improvement when treated early with amino acids serine and glycine (5-7).

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No.

## Conflicts of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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