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Neu-Laxova syndrome: A terrible phenotypic appearance caused by an undefined genetic alteration

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Neu-Laxova syndrome (NLS) is a rare, uniformly lethal congenital disease characterized by abnormalities of placentation, marked intrauterine growth retardation (IUGR), limb contractures, edema, ichthyosis, central nervous system (CNS) developmental defects and unique facial appearance. The degrees and presence of these findings are variable in reported cases. Therefore the differential diagnosis includes very different disorders.Data from the previously described cases in the literature suggest that this disorder is inherited in an autosomal recessive manner and represents heterogeneous genetic alterations.

We herein present a stillborn female at 31 weeks of gestation to consanguineous parents who had one previous offspring affected with non-immune hydrops fetalis. She had typical facial features including severe proptosis with ectropion, micrognathia, flattened nose, gaping mouth and malformed ears. In addition limb deformities and skin lacerations resulting from severe skin restriction were determined. Absence of CNS malformations was the most different feature of reported case.

In this report, we aimed to call attention that 6.25% of all reported NLS cases are Turkish and to date most reported cases were from the countries that have high rates of consanguineous marriage such as Turkey. We emphasized that consanguinity could increase the risk of inheriting of NSL for both the partners to share the same `silent' heterogenic alteration. Early diagnosis with genetic counseling and serial ultrasound examination at risk families is necessary because termination of pregnancy for this lethal condition can be offered.

Keywords: Neu-Laxova syndrome, ichthyosis, skin restriction, terrible facial appearance, undefined genetic alteration.

Background

Neu-Laxova Syndrome (NLS) is a rare, fatal congenital disease that was firstly described by Neu et al. in 1971.[1] One year later, Laxova reported three similar siblings whose parents were first cousins.[2,3] Intrauterine growth retardation (IUGR), abnormal limbs and restrictive dermatopathy were common findings in all these cases.[1–4] The most conspicuous feature of this syndrome is the terrible face with prominence of the eyes (exophthalmos), absence of the eyelids, flattened nose and gaping mouth.[1–5] Until 2005, 64 cases of NLS have been reported in the medical literature.[2–4] Most authors pointed out the usefulness of ultrasonographic investigation in the prenatal diagnosis of this disorder.[1–7] The ultrasonography is especially suggested for monitoring of 'at risk' pregnancies.[6,7] Although inheritance is

claimed to be autosomal recessive, the genetic alteration for NLS has not been yet identified.[2–4]

We present a new case of this rare disorder and review the previously reported cases. We also go into the question of whether or not consanguineous marriage is an accelerative influence on the NSL.

Case

A female stillborn fetus with multiple congenital anomalies was delivered vaginally by a healthy 23-year-old gravida 2 para 0 woman who submitted at 31 weeks of gestation in active labor. Although the parents were first cousins and had one previous offspring affected with non-immune hydrops fetalis and with similar terrible phenotypic appearance; they were not informed about the possibility of prenatal diagnosis of genetic diseases and about the necessity of follow-up during the next pregnancies. So they have not received some kind of formal genetic counseling. When just the contractions began at 31 week of gestation, she submitted to the hospital. Therefore no prenatal ultrasound examinations were performed before delivery.

At autopsy, the infant displayed mild IUGR[8] (Figure 1). Weight was 1350 g, length was 39 cm and head circumference was 27 cm. All body measures appropriated for 10–25th percentile of 31-week-gestation. Moderate subcutaneous edema was noted. Microcephaly was absent and neuropathology examination revealed the normal development pattern of all intracranial structures. The ears were thickened but normally placed. She has the unique face appearance (Figure 2). The eyes were hyperteloric and proptotic without apparent eyelids, the nose was flattened, the mouth was round and gaping with thick everted lips. Moderate micrognathia was determined. Thoracic and abdominal organs were normally oriented, but the lungs were hypoplastic. The extremities demonstrated flexion contractures, bilateral talipes equinovarus and hands fixed in a clenched position (Figure 3). The skin was taut, shiny, and thickened diffusely over the body with fissuring at the axillae, groin, and anal region (Figure 4). Histologically, the skin demonstrated extensive hyperkeratosis and papillomatosis (Figure 5). On the genetic examination, it was demonstrated a normal 46, XX female karyotype. Based on the clinical features, a diagnosis of NLS was made.

Figure 1. Thirty-one week female fetus with NLS.

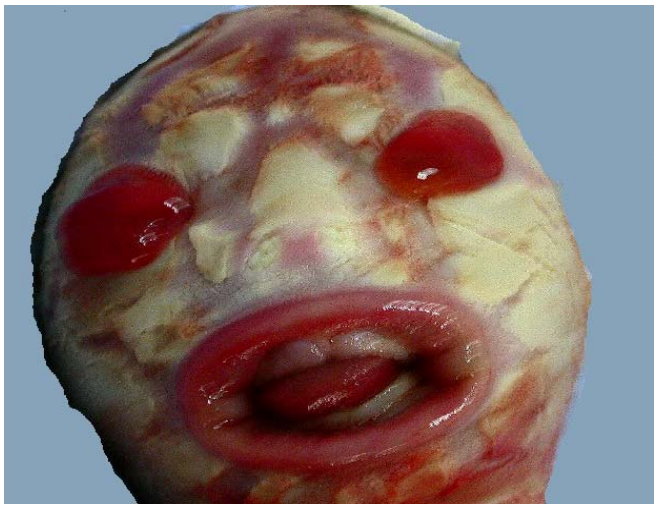

Figure 2. Terrible face appearance with proptosis, flattened nose, gaping mouth and dysplastic ears.

Discussion

Ten years after the first definition of this syndrome, Scott et al.[9] reported further cases bringing the total to 13 and summarized the components of this syndrome as follows: abnormalities of placentation, severe intrauterine growth retardation, edema, ectodermal dysplasia, and the severe CNS developmental defect. In addition, it was suggested that there may be different subtypes of this syndrome, each caused by mutation in a separate gene. In 1982, Curry et al.[2,10] separated the patients into three groups based on skin, limb, and radiographic findings: Group 1 cases have joint contractures, partial syndactyly, scaly skin, and

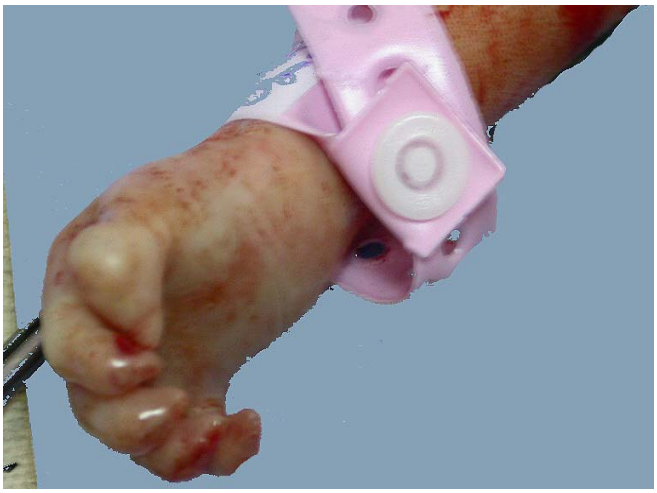

Figure 3. Skin edema and flexion contractures of hand.

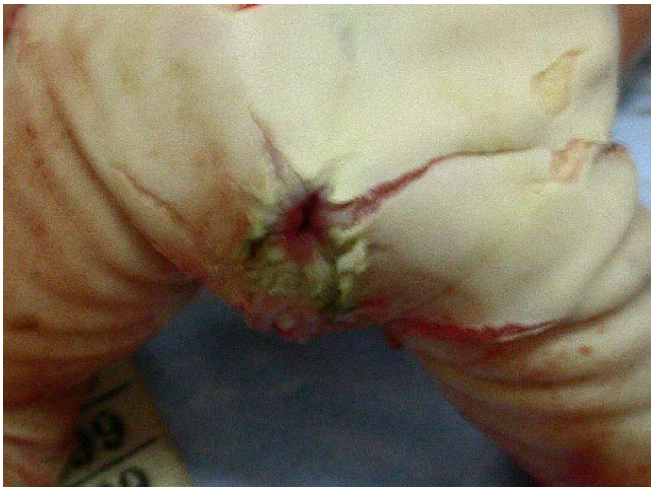

Figure 4. Lacerations resulting from marked skin restriction.

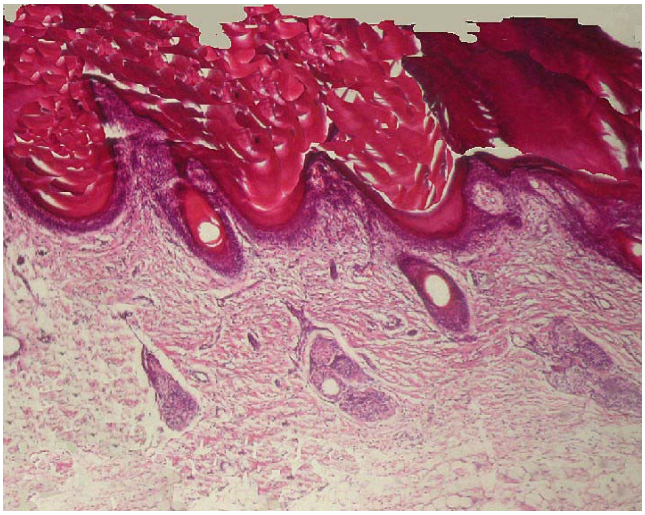

Figure 5. Ichthyosis-like skin features: Extensive hyperkeratosis, papillomatosis and hyperkeratotic plugging (Hematoxylen-Eosin x 100).

poor bone mineralization; group 2 cases present ichthyosis, massive swelling of hands and feet secondary to excess fat deposition-edema; and group 3 cases show the ichthyotic skin lesions as a prominent characteristic change and they have limb contractures with hypoplastic digits and short limbs. There is no consensus about this classification in the literature and most authors suggest the observed variations in phenotype may simply represent different grades of severity of a heterogeneous condition.[2] Central nervous system (CNS) findings are variable and may be more prominent in some patients.[1–5] For example, a 39-week fetus reported by Lazjuk[11] had a brain that weighed only 19.8 g, the smallest recorded weight for brain. In the present case, we did not determine CNS malformations and according to Curry's classification, our case resemble to group 2 cases. Therefore, many syndromes presented with CNS malformations were not considered in the differential diagnosis of reported case.

The underlying pathogenesis NLS still remains unknown.[2–4] But most authors have suggested that NLS may be a complex neuro (oculo) ectodermal dysplasia-mesenchymal dyshistogenesis syndrome.[2] Several hypotheses have been proposed for symptoms in this condition. Karimi-Nejad et al.[5] claimed that many features may be caused by ichthyotic skin changes. Protein loss through the skin lesions can create in utero hypoproteinemia and polyhydramnios, generalized edema and swollen limbs might be secondary to this loss. This hypothesis has not proved and some authors opposed this theory. For example Manning et al.[2] claimed that other ectodermal disorders did not display resembling findings. Most anomalies observed in NLS may be attributed to armor like skin and decreased fetal movement. The characteristic features of NLS simply resemble "restrictive dermopathies". Limb deformities were not a primary defect of mesenchymal tissues development, but rather a consequence of severe cuteneous constraint. Because of tight skin, fetal movement decreases, swallowing fails and contractures develop. Polyhydramnios, limb malformations and terrible face appearance result from this restriction. The affected infant looks like the harlequin fetus caused by this constraint and ichthyosis.[12,13] Contrary in conventional

restrictive dermopathies, only fixed facial expression caused by abnormal collagen and keratin syntheses is noted. Typical and diagnostic facial appearance is peculiar to the NLS.[13]

All cases in which chromosome analysis has been performed karyotype results are normal.[1–7] Similarly, our case demonstrated a normal karyotype. Still no genetic alterations had been found that would lead to disruption of a gene likely to be a candidate to explain the findings in NLS.[2] However it has been shown in recent animal trials that the genes associated with epidermal differentiation on human chromosomes 6q and 9p must be investigated fastidiously.[2,14]

Around the globe consanguineous (blood-related) marriages have been practiced by many societies such as Asia, North Africa, Switzerland, Middle East, some parts of China, Japan and fishermen communities in Europe and America from time immemorial. Several scientific studies have shown that consanguinity may lead to genetic diseases.[15] Due to the inheritance parents and children, and brothers and sisters, commonly share 50 per cent of their genetic make-up. Similarly uncle and niece share 25 per cent and first cousins 12.5 per cent of their inherited genetic material as it originates from a common ancestor. In such situations if there are any 'silent' genetic defects, then probability of errors manifesting as a disease in the child of a consanguineous parents is high. Consanguineous marriage is also a widely practiced social custom in Turkey.[11] Different nationwide surveys indicated that this rate was 20–25% and having increased over the last 20 years.[15] The rate of consanguinity among parents of children with rare recessive diseases is quite above of Turkey's average and the high consanguinity rate may be one of the underlying factors of increased case number with some rare congenital disorders such as NLS. Until 2005, we found reports of 64 purported cases of NLS and 6.25% of them are Turkish. Striking data about NLS in the literature is most cases were from the countries mentioned above that have high rates of consanguineous marriage such as Turkey.[1–7] Finally, we think that considerable attention must be paid to the role of consanguineous marriage as a causative factor in the prevalence of NLS.

The prenatal ultrasound findings of marked ocular proptosis in a growth-restricted, edematous fetus, abnormal fetal movement should prompt consideration of the diagnosis.[2,3,6] The usefulness of ultrasonographic demonstration of no breathing movements, no sucking, and no swallowing at 34, 35, and 36 weeks' gestating in the prenatal diagnosis of this disorder is pointed out.[6] Also there were no hiccups or normal isolated arm or leg movements.[2,3] Prenatal diagnosis and termination of pregnancy in the NLS are suggested approach. But prenatal diagnosis is related to socio-economic background and education.

Therefore, for prevention of NLS, the emphasis in Turkey has probably to be placed on public awareness about genetic risks, the risks of consanguinity, availability of genetic counseling, while taking into consideration the religious beliefs and education of the target population. In conclusion, early diagnosis in NLS with genetic counseling and serial ultrasound examination at risk families is essential to terminate the pregnancy.

References

1. NeuRL, Kajii T, Gardner LI, Nagyfy SF. A lethal syndrome of microcephaly with multiple congenital anomalies in three siblings. Pediatrics 1971; 46: 610- 612.
2. Manning MA, Cunniff CM, Colby CE, El-Sayed YY, Hoyme HE. Neu-Laxova syndrome: detailed prenatal diagnostic and post-mortem findings and literature review. Am J Med Genet 2004; 125 : 240-249.
3. Aslan H, Gul A, Polat I, Mutaf C, Agar M, Ceylan Y. Prenatal diagnosis of Neu- Laxova syndrome: a case report. BMC Pregnancy Childbirth 2002; 2: 1.
4. Mihci E, Simsek M, Mendilcioglu I, Tacoy S, Karaveli S. Evaluation of a fetus with Neu- Laxova syndrome through prenatal, clinical and pathological findings. Fetal Diagn Ther 2005; 20: 167- 170.
5. Karimi-Nejad MH, Khajavi H, Gharavi MJ, Karimi-Nejad R. Neu-Laxova syndrome: report of a case and comments. Am J Med Genet 1987; 28: 17- 23.
6. Shapiro I, Borochowitz Z, Degani S, Dar H, Ibschitz I, Sharf M. Neu-Laxova syndrome: prenatal ultrasonographic diagnosis, clinical and pathological studies, and new manifestations. Am J Med. Genet 1992; 43: 602-605.
7. Driggers RW, Isbister S, McShane C, Stone K, Blakemore K. Early second trimester prenatal diagnosis of Neu-Laxova syndrome. Prenat Diagn 2002; 22: 118- 120.
8. Stocker JT, Dehner LP. Appendices. In: Pediatric Pathology, 2.ed. Lippincott, Williams, Wilkins. Philadelphia 2001, 1403-1528.
9. Scott CI, Louro JM, Laurence KM, Tolarova M, Hall JG, Reed S, Curry CJR. Neu-Laxova Syndrome and CAD complex (Letter). Am J Med Genet 1981; 9: 165-175.

10. Fitch N, Curry CJR. Comments on Dr. Curry's classification of the neu laxova syndrome (letter). Am J Med Genet 1983; 15: 515- 518.
11. Ostrovskaya TI, Lazjuk GI. Cerebral abnormalities in the neu-laxova syndrome. Am J Med Genet 1988; 30: 747- 756.
12. Hickey P, Piantanida E, Lentz- Kapua S, Kenner J. Neu- Laxova Syndrome: a case report. Pediatr Dermatol 2003: 20: 25-27.
13. Thakur S, Pal L, Phadke SR. Lethal arthrogryposis with icthyosis: overlap with Neu-Laxova syndrome, restrictive dermopathy and harlequin fetus. Clin Dysmorphol 2004; 13: 117- 119.
14. Tuncbilek E. Clinical outcomes of consanguineous marriages in Turkey. Turk J Pediatr 2001; 43: 277- 279.
15. Fisher C. IKK$\alpha^{-/-}$ mice share phenotype with pupoid fetus (pf/pf) and repeated epilation (Er/Er) mutant mice. TIG 2000; 16: 482-484.