Prenatal diagnosis and postmortem findings of Neu-laxova syndrome

Neu-laxova sendromunun prenatal tanısı ve postmortem bulguları

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Abstract

Neu-laxova syndrome is a lethal, autosomal recessive condition associated with ectodermal abnormalities and other characteristic features, including microcephaly, marked intrauterine growth restriction, limb deformities, central nervous system malformations and abnormal facial features, consisting of severe proptosis with ectropion, hypertelorism, micrognathia, flattened nose, malformed ears, and gaping mouth. Here we present a fetus having a dysmorphic face with proptotic eyes, retracted eye lids, depressed nasal bridge and micrognathia at 25 weeks of gestation. The extremities were contracted and no fetal movements were observed during the ultrasonographic examination. The fetus also had microcephaly and the amniotic fluid was increased. The pregnancy was terminated and the abnormalities demonstrated on prenatal ultrasound were confirmed at autopsy.

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Özet

Neu-laxova sendromu yaşamla bağdaşmayan, otozomal resesif bir hastalıktır ve ektodermal anormalliklerle birliktelik gösterir. Diğer karakteristik özellikleri; mikrosefali ile birlikte belirgin gelişme geriliği, ekstremite deformiteleri, santral sinir sistemi anormallikleri ve anormal yüz görüntüsü, ektropiyon ile birlikte ciddi proptozis, hipertelörizm, mikrognati, düzleşmiş burun sırtı, malforme kulaklar ve açık ağızdır. Bu vaka sunumunda 25. gebelik haftasında propitotik gözle birlikte dismorfik yüz, retrakte göz kapakları, düzleşmiş burun sırtı ve mikrognatinin eşlik ettiği fetal anomaliyi sunduk. Ultrasonografik incelemede ekstremitelerin kontrakte olup, fetal hareket hiç izlenmedi. Fetusun ayrıca mikrosefalisi olup, polihidramniosu mevcuttu. Gebelik termine edildi ve prenatal dönemde ultrasonografi ile tespit edilen bulgular otopsi ile konfirme edildi.

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Anahtar kelimeler: Neu- laxova sendromu

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Introduction

Neu-laxova syndrome (NLS) is a rare, autosomal recessively inherited syndrome characterized by intrauterine growth restriction (IUGR), central nervous system (CNS), and skin and limb abnormalities (1, 2). Here we present a fetus with this syndrome with a description of its prenatal and postmortem findings.

Case report

A twenty seven year old G2 P2 pregnant woman was referred with a presumed diagnosis of fetal anomaly. She did not report for the routine antenatal follow-up. Her previous history was unremarkable except for first degree consanguinity with her partner. She did not report any drug use or radiation exposure. The last menstrual period was uncertain.

At the ultrasound examination; the fetus had a biparietal diameter and head circumference concordant with 22 weeks, and an abdominal circumference and femur length with 25 weeks (estimated gestational age was 23,5 weeks according to the ultrasound measurement). Microcephaly was prominent. The forehead was sloping, the eyes markedly proptotic, intraorbital distance was15 mm, extraorbital distance measured 46mm The mouth was gaping and micrognathia was present (Figure 1). Cardiac examination was normal,but the stomach was not visible. The penis was 7, 9 mm, (<10 p), giving the impression of ambiguous genitalia (Figure 2) (3). The hands were clenched, the elbows and the hips were flexed, the

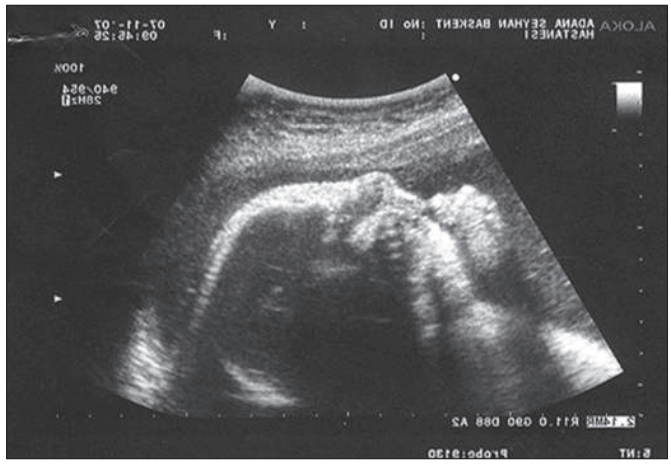

Figure 1. Abnormal facial profile on ultrasound

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knees hyperextended. The feet seemed dysmorphic. The fetus did not move during the 30 minute examination. The amniotic fluid was increased and 82 mm by single pocket measurement. To exclude a chromosomal abnormality, a cordocentesis was performed which revealed a normal male karyotype. At this time, the diagnosis ofNLS was strongly suspected. The poor prognosis was discussed with the couple and they opted for termination. At the post mortem examination the skin was thick. The baby seemed to be covered by a thick membrane. Microcephaly and micrognathia were present. The eyes were proptotic with almost no eyelids. The nasal ridge was broad, ears were low set (Fig. 3) with multiple bilateral contractures present at the extremities. The arms were flexed at the elbows, the hands were clenched. The legs were flexed at the hips and hyperextended at the knees (Fig. 4). The external genitalia had a male appearence;however, the thick skin covering the genitalia gave the impression of ambiguous genitalia (Fig. 5).
At autopsy, the confirmed the sonographic findings of microcephaly, proptotic with mild ocular hypertelorism, microphthalmia, an open mouth, micrognathia, a flattened nose, low set ears, very short neck and abnormal joint positioning, as predicted by ultrasound. The penis and scrotum were hypoplastic. The skin was thick, shiny and peeling in places, and this was specially marked on the trunk and inguinal regions. Histological section of the skin demonstrated a thick, compact hyperkeratosis with a normal granular layer, and dermal edema, and increased subcutaneous fat (Fig. 6). Hair follicles and subcutaneous glands were present. Additionally, the lungs were hypoplastic. No cardiac or renal abnormalities were found.
Neuropathololgic examination revealed a brain weight of 22.5 g, with post-fixation weight 11.2 g (concordant with $<20^{th}$ weeks). On gross examination, the surface of the brain was smooth and the gyral pattern was poorly developed, with a limited number of well-formed gyri. The cerebellum was normal. The ventricular system was dilated, especially the occipital horns of the lateral ventricles. Cortical parenchyma was thinned in the occipital lobe adjacent to the ventricules. Histological examination of the brain revealed findings of focal neuronal migration disorder.
Based on the clinical and histopathological findings, a diagnosis of NLS was made.

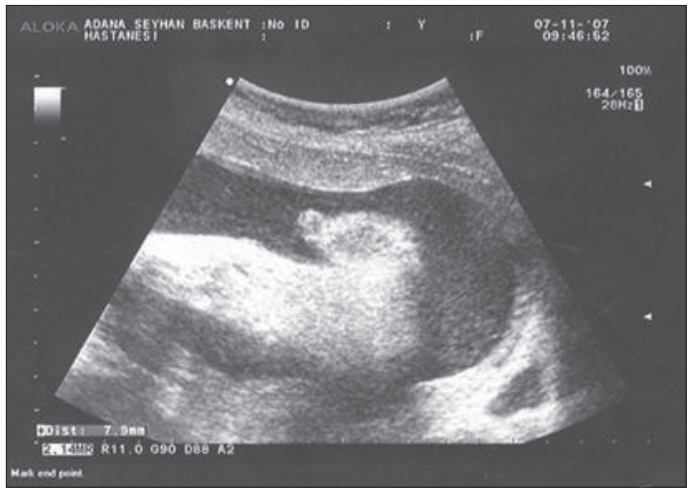

Figure 2. Ultrasonographic appearance of external genitalia

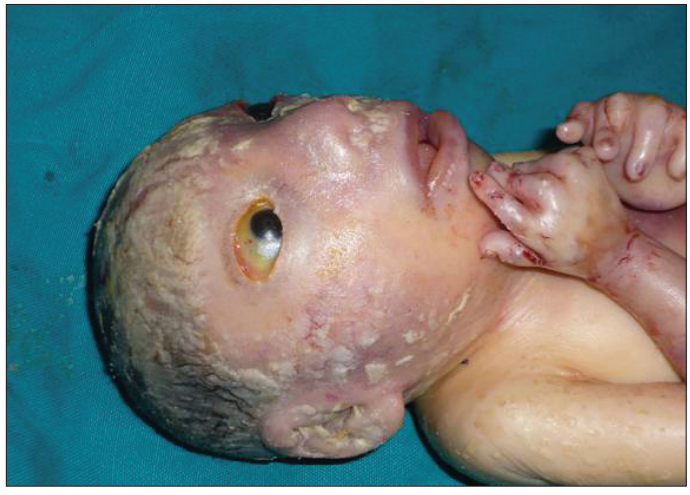

Figure 3. Proptotic eyes with almost no eyelids and broad nasal ridge at postmortem examination

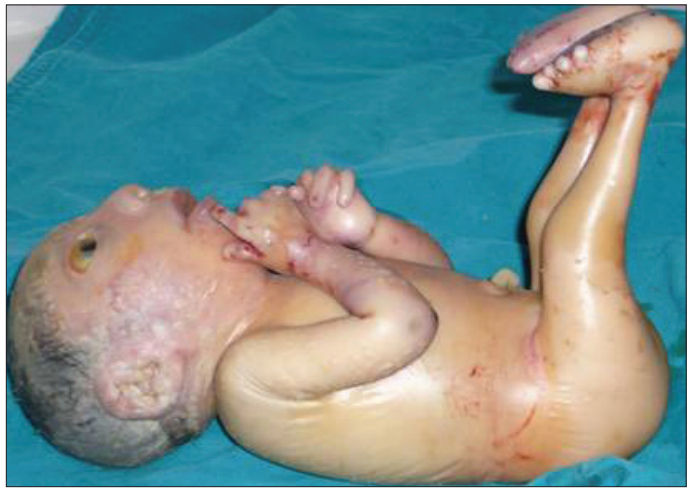

Figure 4. The legs were flexed at the hips and hyperextended at the knees

Discussion

Neu-laxova syndrome is an autosomal recessively inherited, lethal syndrome characterized by intrauterine growth restriction, CNS abnormities and skin disease (1, 2). Microcephalies, sloping forehead, ocular hypertelorism, exophthalmus, flat nasal bridge, lowset ears, micrognathia, a gaping mouth with everted lips and flexion contractures are the main features of the syndrome. It is invariably fatal. The CNS defects, pulmonary hypoplasia and infection are thought to be responsible for the short survival of these infants. IUGR, swollen limbs, poor bone mineralization and short survival can also be caused by the loss of protein through skin fissures (1, 4).
CNS anomalies, skin disease and limb contractures are the main features in NLS. Among the reported CNS abnormalities are lissencephaly, dilated ventricles, absent corpus callosum, absent or small anterior fontanel, calcifications, cerebellar defects (4).
The characteristic limb posture is flexed elbows, wrists, clenched hands, flexed hips and hyperextended legs. Syndactyly, brachidactyly, overlapping digits, webbing, vertebral anomalies, flexion deformities and poor bone mineralization are common

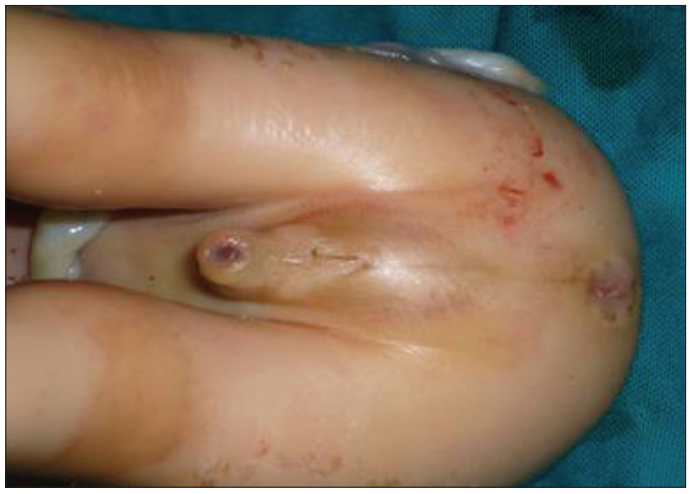

Figure 5. External genitalia at post mortem examination

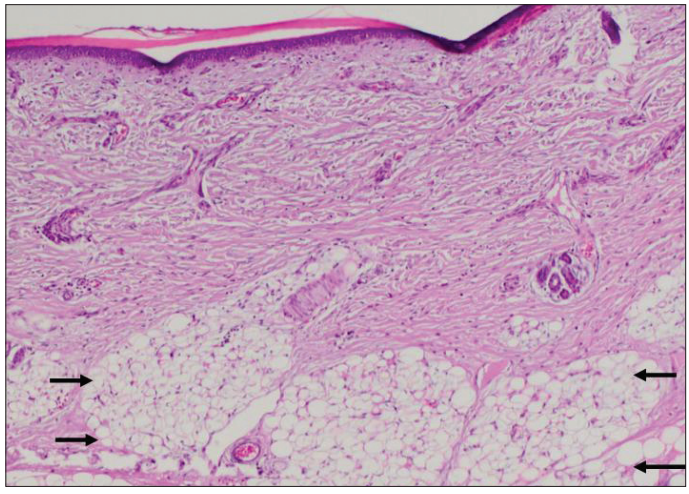

Figure 6. Skin biopsy specimen revealed a thick, compact hyperkeratosis with a normal granular layer. Deposition of fat in the dermis (arrows). [Hematoxylin and eosin (H&E)x100]

features of these fetuses (5).

NLS is characterized by a yellow, scaling ichthyosis or a taut, shiny, incomplete, collodion like membrane involving the upper body. In approximately 40% of the cases, the skin disease manifests itself as ichthyosis. The skin looks taut and shiny, reminiscent of restrictive dermopathy (6).

The differential diagnosis includes severe arthrogryposis syndromes such as cerebro-ocular-facial-skeletal (COFS) syndrome, the lethal multiple pterygium syndrome, restrictive dermopathy, fetal akinesia/ hypokinesia sequence, cerebro-arthro-digital syndrome, Harlequin fetus, Smith- Lemli- Opitz syndrome and Miller – Dieker syndrome (4, 7, 8).

Microcephaly with brain hypoplasia, flexion contractures, and micrognathia are also seen in COFS syndrome, but the typical, deep set eyes with blepharophimosis and prominent root of the nose are very different from the protruding eyes and flattened nose seen in NLS. The lethal multiple pterygium syndrome shares many abnormalities with Neu-laxova, such as flexion contractures, and prenatal onset growth deficiency, but the pterygia bridging of virtually all joints seen in this syndrome was not present in our case. Intrauterine growth restriction, hypertelorism, micrognathia, and joint contractures are also seen in restrictive dermopathy, but the rigid and tense skin, small “pinched” nose, and small mouth also associated with this disorder were not seen in our case (6).

Fetal akinesia/ hypokinesia sequence (Pena-Shoiker) demonstrates pulmonary hypoplasia, limb deformities, and a facies similar to NLS, but lacks CNS and skin manifestations (8).

Harlequin fetus is a lethal condition with ichthyosis, eclabion, ectropion, and limb contractures similar to NLS. Absence of severe microcephaly and CNS abnormality in Harlequin fetus may help in differentiating the NLS (7).

Smith- Lemli- Opitz syndrome is characterized by prenatal and postnatal growth retardation, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the second and third toes and severe mental retardation. Miller-Dieker syndrome is characterized by microcephaly, lissencephaly, pachygyria, narrow forehead, hypoplastic male external genitalia, growth retardation, seizures and profound mental retardation. Microcephaly and IUGR are features of both Smith- Lemli- Opitz and Miller-Dieker syndromes (9). However, specific findings such as severe microcephaly, ichthiyosis, and peculiar face and cerebral anomalies are sufficient elements to differentiate NLS from other syndromes, as in our case.

In conclusion, NLS is a rare and uniformly lethal disorder characterized by multiple abnormalities. Since the prognosis is extremely poor, prenatal diagnosis is important. Counseling is mandatory for the affected consanguineous couples, as autosomal recessive inheritance with a 25% recurrence risk is obvious (10).

Conflict of interest

No conflict of interest is declared by authors.

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