Common Benign Dermatoses and Birthmarks in the Neonatal Period: Medical Education

Neonatal Dönenme Sik Görülen Benign Dermatozlar ve Doğum İzleri

ABSTRACT Neonatology represents one of the subspecialties of pediatrics and there are skin conditions in the neonatal period, which need prompt recognition by both neonatologists and pediatric dermatologists. Premature skin immaturity in the neonatal period is associated with transient benign dermatoses; birthmarks some of which may require further work-up for underlying defects or malignant potential may cause considerable confusion in the neonatal period. This article focuses on proper diagnoses of these dermatoses and birthmarks in order to reassure the parents and initiate further evaluation if there are risks for complications or malignant transformation.

Key Words: Infant, newborn; skin; skin diseases

ÖZET Neonatoloji pediatriünün yan dal uzmanlık alanlarından biri olup, bu dönemde pediatrik dermatologların da neonatologlar ile birlikte kısa sürede tanı koyması gerektiren deri ile ilgili durumlar bulunmaktadır. Neonatal dönemdeki prematur deri immaturitesi geçici benign dermatozlar ile ilişkilidir; ayrıca, bazılarında altta yanatan defektiler veya malignite gelişme riski nedeni ile ileri araştırma gerekebilen doğum izleri, neonatal dönemde önemli karşılıklara yol açabilir. Bu çalışmada, ebeveynlerin endişelerini gidermek üzere neonatologlar ve pediatrik dermatologların bu dermatozların ve doğum izlerinin doğru tanılarını koymalarını yardımcı olmak, ayrıca ortaya çıkabilecek komplikasyon ve malign tranformasyon açısından gerekli olabilecek ileri değerlendirilmelere ışık tutmak üzere derlenmiştir.

Anhahter Kelimeler: Yenidoğan; deri; deri hastalıkları


The neonatal period is defined as the first 4 weeks of life.¹ The skin of preterm and term neonates manifests several significant differences that distinguish it from mature adult skin and experiences morbidity caused by compromised skin barrier integrity.² ⁴ Most of these differences are benign and self-limited, but they must be differentiated from unusual presentations or signs of systemic illnesses.⁵ Congenital patterns of abnormal pigmentation or vascular proliferations manifesting as birthmarks may represent isolated phenomena but may also act as markers for a variety of systemic disorders, and some may require further work-up for underlying defects or malignant potential.² ⁶ This article reviews the most common benign transient dermatoses and birthmarks encountered in the neonatal period, their diagnoses, and management.
**BENIGN TRANSIENT DERMATOSES**

**ERYTHEMA TOXICUM NEONATORUM**
Erythema toxicum neonatorum (ETN) occurs in up to 60% of term newborns, equally in boys and girls, but is uncommon in premature infants. Although delayed onset on the twelfth day of life has been observed, the rash usually arises within the first three days and may also be present at birth. Erythematous macules, wheals, and vesiculopustules, usually arising from an erythematous base, are the typical skin lesions (Figure 1). They can occur almost anywhere on the body, but palmoplantar and perioral sparing is diagnostic.7-9 A minor graft-versus-host (GVH) reaction, caused by maternofetal transfer of lymphocytes prior to or during delivery, and early microbial exposure of the newborn are the proposed etiologies.10,11 The diagnosis is usually made clinically, but if needed pustular smear shows eosinophilia on cytologic examination.12 ETN resolves spontaneously without treatment within five to seven days.5,13

**TRANSIENT PUSTULAR MELANOSIS**
Transient pustular melanosis (TPM) which occurs in 5% of term black infants and less than 1% of white infants is a self-limiting dermatosis of unknown etiology. The eruption is always present at birth or within the first 24 hours.7,14 Superficial pustules and pigmented macules are located on the face, limbs and back. Contrary to ETN, palms and soles are often involved. Sometimes, only pigmented macules are already present at birth. Pustules subside leaving either a brownish crust or a scaling edge.15-17 Cultures are negative but the lesions are found to contain polymorphonuclear leukocytes on cytologic examination. The macules usually resolve within three months without treatment.14 But a clear-cut differentiation between TPM and ETN is not always possible and it needs to be determined whether this is really is just an early-onset variant of ETN occurring in the dark-skinned newborns.18,19

**MILIARIA**
Miliaria crystallina and miliaria rubra, the most common types in the neonatal period result from obstruction and rupture of the eccrine sweat ducts. Miliaria crystallina is an asymptomatic eruption characterized by 1–2 mm clear vesicles, which rupture easily. It reflects the obstruction of the sweat duct within the stratum corneum. Fever and a warm, humid or overheated environment are the precipitating factors.19,20,21 Miliaria rubra occurs later than miliaria crystallina, mostly in hot humid conditions. It usually affects sites of friction or occlusion such as the neck, face and the trunk. Lesions are 1–3 mm erythematous papulovesicles and the level of ductal obstruction is intraepidermal.21 Spontaneous resolution can be achieved by controlling ambient temperature and humidity.22
SEBACEOUS HYPERPLASIA

Most of the full-term infants have multiple tiny white or yellow spots involving the pilosebaceous follicles of the nose, forehead, upper lip and malar areas. The lesions which resolve in 2 to 3 weeks of age are manifestation of maternal androgen stimulation and are rarely seen in preterm infants.23,24

MILIA

Milia are firm white papules 1 to 2 mm in diameter. Histologic examination reveals miniature epidermal inclusion cysts. They are very common on the face of full-term newborns and are of no consequence in this population they usually disappear within a few weeks.7,25

EPSTEIN PEARLS

Epstein pearls are lesions similar to milia, which may appear inside the mouth around the junction of the soft and hard palate in most neonates. They usually disappear spontaneously.13,24

SUCKING BLISTERS

Sucking blisters result from the friction of repeated sucking in utero or in early infancy, particularly on a finger, hand, or lip. They are self-limiting and do not require therapy. The location, noninflammatory nature of the clear blister, and lack of associated blisters or vesicles are reassuring.22,24

ACNE NEONATORUM

Acne neonatorum, which occurs in up to 20% of newborns, typically consists of closed comedones on the forehead, nose, and cheeks. Open comedones, inflammatory papules, and pustules may also develop (Figure 2). Neonatal acne is thought to result from stimulation of sebaceous glands by maternal or infant androgens. The lesions usually resolve spontaneously within four months without scarring. Treatment generally is not necessary, but the infants can be treated with a 2.5% benzoyl peroxide lotion if lesions are extensive and persist for several months. If the acne lesions are severe and are accompanied by other signs of hyperandrogenism, the patient should be investigated for adrenal cortical hyperplasia, virilizing tumors or underlying endocrinopathies.12,26 Acne infantum is a rare skin disorder that predominantly affects males and frequently manifests in the first 6 to 9 months of life. Unlike acne neonatorum, it can persist and may be considered a predictor of severe acne juvenilis.27,28 Also, severe cases of acne infantum may lead to scarring.27,29,30

On the other hand, some confusion exists as to whether acne neonatorum truly exists or it is in fact neonatal cephalic pustulosis, which is an inflammatory response to Malassezia species. However, some of what is termed acne neonatorum is an early presentation of comedonal acne and not a response to Malassezia, and more studies are needed to define the clinical characteristics and pathogenesis of both conditions.31

BIRTHMARKS

NEVUS SEBACEOUS

Nevus sebaceous (NS) which is seen in 0.3% of newborns is a common congenital condition, typically presenting at birth as a single hairless, linear or less commonly round, somewhat yellow plaque, on the face or scalp.32-34 It persists throughout life but tends to become warty and raised at puberty. A variety of benign neoplasms such as trichoblastomas, syringocystadenoma papilliferum, nodular hidradenoma, apocrine cystadenoma, tricholemmoma, tumor of the follicular infundibulum, and malignant neoplasms such as basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, and apocrine carcinoma can develop from NS. Although it has also been reported that malignant neoplasms in children with NS are extremely rare and clinical follow-up is probably sufficient, complete prophylactic excision of NS is recommended before puberty, as the risk of malignancy increases with age.34-36

MONGOLIAN SPOTS

Mongolian spots are waxy bordered and irregular shaped birthmarks in blue or slate-gray color with varying sizes. They are caused by the arrest of melanocytic migration in the dermis of the embryo and may become darker in color. Among different ethnic groups, over 90% of Native Americans and people of African descent, approximately 70% of Hispanics and 80% of Asians, and fewer than 10%
of Caucasians have Mongolian spots. They are typically lumbosacral in location and present at birth (Figure 3). In most instances, this pigmentation stabilizes in infancy and then spontaneously regresses during childhood. They should be differentiated from nevus of Ito and nevus of Ota, which are characterized by benign melanosis involving the skin of the acromioclavicular region and the face about the eye, respectively. The skin pigmentation is more diffuse and less mottled and does not regress by age in nevus of Ito and Ota.

**CAFE-AU LAIT MACULES**

Histologically, cafe-au-lait macules (CALMs) represent localized areas of increased melanin content in melanocytes and basal keratinocytes without an increase in the number of melanocytes. CALMs are well circumscribed, uniformly light to dark brown macules averaging 2-5 cm in adults. They can be present at birth but they usually develop during early childhood and grow proportionately to body growth (Figure 4). Isolated CALM is a common finding in 10-20% of normal healthy young children. Having six or more CALMs is one of the seven cardinal criteria for the diagnosis of neurofibromatosis type-1 (NF1). However, the CALMs are not pathognomonic for NF1 as they also have been reported clinically in other disorders like McCune Albright syndrome, tuberous sclerosis or Leopard syndrome.

**CONGENITAL MELANO CYTIC NEVI**

A congenital melanocytic nevus (CMN) is a benign proliferation of cutaneous melanocytes, which is clinically apparent at birth or becomes so within the first postnatal weeks. CMN affects approximately one percent of all newborns. Generally, CMNs are round to oval in shape and have a regular, smooth, and well-demarcated border. In neonates, they may be light in color and relatively hairless, with a flat or raised surface. As the child grows, the nevus may become progressively darker, and may acquire darkly pigmented hairs. CMNs may exhibit a papular, rugose, pebbly, verrucous, or cerebriform surface.

Scoliosis, spina bifida, atrophy, asymmetry, clubfoot, elephantiasis, and cranial bone hyper-

trophy are the developmental abnormalities associated with CMN. Neurocutaneous melanosis is a rare congenital disorder characterized by the presence of giant or multiple melanocytic nevi associated with benign or malignant melanocytic tumors of the central nervous system. Patients with large or multiple congenital nevi on the head, neck, or posterior midline seem to have an increased risk for neurocutaneous melanosis, and they should be monitored for any signs or symptoms of increased intracranial pressure, mass lesions, or spinal cord compression.

The risk of melanoma arising from a CMN is highest in giant congenital nevi (≥20cm; 2%-30%), although it has been documented also in small and intermediate melanocytic nevi. The cumulative melanoma risk is estimated to be 2.6% to 4.9% for persons with small CMNs who live up to 60 years of age. The risk of melanoma in giant CMN appears to be greatest in the first decade of life and prophylactic excision is recommended as early as possible. Lifelong observation with medical follow-up can be performed if the nevus is small and regular. However, since the risk of melanoma rises with the onset of puberty, excision of small and intermediate CMN around the pubertal years is recommended if the nevus is irregular or is located in a site that is hard to follow up. Generally, management decisions for CMN, regardless of its size, should take into consideration the perceived risk of melanoma, the patient’s age, the cosmetic outcome, the surgical complexity, and the risk of anesthesia.

**LEUKODERMAS**

Piebaldism is a congenital autosomal dominant stable pigmented disorder, characterized by a white forelock and symmetrical depigmented macules involving usually the anterior thorax, the abdomen, and the mid arms and legs. Depigmentation can also be observed on the forehead, in a triangular form. Typically, there are also hyperpigmented macules at the periphery of the depigmented lesions. Piebaldism probably results from mutations of the c-kit proto-oncogene, leading to failure of epidermal melanocytes, which translates into a complete
lack of pigmentation. When a patient presents with a white forelock and/or lesions of piebaldism, it is important to look for signs of the Waardenburg syndrome (WS), such as deafness, heterochromia irides, and facial dysraphism. Occasionally, a patient may have Hirschprung disease (congenital megacolon) in addition to lesions of piebaldism or signs of WS.

When there is a single hypopigmented macule or patch in an otherwise asymptomatic healthy child, the most likely diagnosis is nevus depigmentosus (ND) (Figure 5). ND is a congenital, nonfamilial disorder characterized by a hypopigmented macular lesion that remains stable over time.

Histological examination reveals a normal or decreased number of melanocytes and normal size and melanization of the melanosomes. A defect in the transfer of melanosomes from melanocytes to keratinocytes has been suggested.

The diagnosis of tuberous sclerosis (TS) becomes more likely if there are multiple hypomelanotic macules, patches of poliosis, or the lesions have a lance-ovate shape. A very helpful sign is the presence of multiple hypopigmented “confetti” macules that are 1-3 mm in diameter. Additional cutaneous findings of TS, facial angiofibromas and ungual fibromas are rarely present in children less than 5 years of age. Although cranial computerized tomography scans and magnetic resonance imaging can confirm the diagnosis in approximately 95% of patients, a simple diagnostic tool is echocardiography to detect cardiac rhabdomyomas seen in up to 90% of children less than 2 years of age with TS.

Hypomelanosis of Ito (HI) is characterized by skin hypopigmentation along the lines of Blaschko (Figure 6). This pattern of lines appears as streaks displaying a V-shaped or fountain-like pattern over the spine, an S-shape or whorled pattern over the anterior and lateral aspects of the trunk, and a linear arrangement over the extremities. They represent the orderly migration of mesodermal and ectodermal precursors during embryogenesis. Abnormalities of the karyotype are found in up to
50% of patients. These abnormalities are predominantly mosaicism leading to the generation of two lineages of cells that produce the pattern of pigmented and hypopigmented skin. The skin lesions of HI are usually detected in the newborn period. Histopathologically, there is a decreased number of melanocytes as well as number and size of melanosomes in the basal layer of the epidermis. Hypomelanosis of Ito is most commonly associated with central nervous system abnormalities, particularly developmental delay or mental retardation.

**SALMON PATCH**
The salmon patch is a congenital telangiectatic nevus which occurs in 40% of infants, most commonly as a flat pink macule on the nape of the neck (stork bite), glabella or upper eyelid (angel kiss). Ninety-five percent of salmon patches on the glabella and eyelids disappear within the first years of life, and 50% of the nuchal lesions clear spontaneously (Figure 7). Sometimes the distinction between salmon patch and port-wine stain is not always clear. Glabellar, forehead and upper eyelid salmon patches tend to fade very substantially, but similar lesions elsewhere persist permanently. For this reason, there is a trend towards calling both types of lesion simply “vascular stains”. Recently, both types of lesions have been called “nevus flammeus” but divided into “small” (salmon patch type) and “large” (port-wine type).

**HEMANGIOMA**
Hemangiomas are the most common vascular tumors of infancy, found in up to 10% of Caucasian children. Recently it has been reported that the overall true incidence is estimated to be close to 4-5%. They occur in children of all races, but are less common in those of African or Asian descent. They are 3 to 5 times more common in females and are particularly common among premature infants. Hemangiomas are the result of pathologic angiogenesis and they typically appear shortly after birth (Figure 8). They arise from a somatic mutation, with clonal expansion of the endothelial cells. Increased risk of hemangiomas in mothers who had chorionic villus sampling and shared immunogenicity between placental tissue and hemangiomas led to speculation that some hemangiomas arose from ectopic placenta or a shift of the endothelium to the placental phenotype, although this hypothesis has been challenged.

Hemangiomas of infancy are the most common type of hemangiomas. They appear within the first week of life, have a predilection for the head and neck, and undergo rapid proliferation in the first year, followed by involution beginning by 1 year and continuing over the next to 5 to 10 years. During involution, the superficial component undergoes a color change from bright red to dull red, then to grey; the deep component becomes less blue and less warm but they may also resolve with minor residual changes like telangiectasia, atrophic wrinkling, and discoloration. Non-involuting congenital hemangiomas present as solitary pink to purple tumors, often with coarse telangiectasia on the overlying skin, and have a central or peripheral pallor. They proportionately increase in size with the growth of the child but do not involute. Rapidly involving congenital hemangiomas proliferate in utero, are fully developed at birth and begin to regress during early infancy. Benign neonatal hemangiomatisis is a rare presentation in which multiple small cutaneous lesions are found in the neonatal period but there is an associated risk of visceral involvement (disseminated neonatal hemangiomatisis), especially in the liver and gastrointestinal tract, which may in turn lead to congestive cardiac failure and hemorrhage. Children with PHACES syndrome present with a large facial hemangioma and associated abnormalities which include posterior fossa malformation, arterial anomalies, cardiac anomalies, eye anomalies, and sternal cleft with or without supraumbilical raphe. Lumbosacral hemangiomas can be associated with tethered spinal cord or abnormalities of the anorectal or urogenital regions. These hemangiomas are flat and span the midline. Radiographic studies of the spine and pelvis should be obtained to identify associated anomalies.
Treatment is conservative in the majority of lesions, but ocular, airway or auditory obstruction and congestive heart failure are indications for treatment. First line therapy consists of oral corticosteroids, intraleional corticosteroids, and topical corticosteroids. Second-line therapy includes vincristine, cyclophosphamide, interferon alpha-2a and 2b, vascular specific pulse dye laser, and surgical excision for lesions unresponsive to medical treatments.67

PORT-WINE STAIN
Port-wine stains (PWSs) are capillary malformations seen in approximately 0.3% of newborns. At birth, PWSs are pink to light red macules in which ectatic dermal venules cause the characteristic skin color (Figure 9). As the patient ages, these malformations enlarge proportionally and persist into adulthood, often producing a darker purple lesion with a roughened, cobblestone-like texture.76,77 The pulse dye laser is the treatment of choice for PWSs, with proven efficacy and low incidence of side-effects, preferably early in life to minimize the potential psychological morbidity of disfiguring lesions.78,79
In the neonate, PWS may be a clinical marker for more serious underlying neurologic, vascular, or musculoskeletal abnormalities.\textsuperscript{80} Nearly 50% of all facial PWSs are located in the distribution of the trigeminal nerve. These lesions are often isolated findings but also may be associated with Sturge Weber syndrome, in which patients also have seizures, glaucoma, abnormal cerebral vasculature, and mental retardation.\textsuperscript{81} It is characterized by the association of a facial capillary angioma involving the periorbital area, the forehead and possibly scalp, and an underlying leptomeningeal angioma. The condition is sporadic with no evidence of genetic determinants, and neuroimaging is diagnostic.\textsuperscript{61}

Klippel-Trenaunay syndrome (KTS) is a multi-system disorder possibly resulting from a pathogenic gene for vascular and tissue overgrowth. It consists of varicose veins, a cutaneous capillary malformation, and hypertrophy of bone and soft-tissue. A PWS, which is often noted at birth, is often the first abnormality to be recognized in patients with KTS.\textsuperscript{82}

Proteus syndrome (PS) is a rare, sporadic overgrowth disorder that is probably caused by a somatic mosaicism lethal in the nonmosaic state.\textsuperscript{83} The clinical presentation is variable, but the course is progressive. The main clinical features are limb asymmetry with asymmetrical overgrowth of the hands and/or feet, macrodactyly, connective tissue nevi, epidermal nevi, lipomas, vascular malformations and cranial hyperostoses.\textsuperscript{84}

REFERENCES


