Pediatric Acne

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Abstract
Acne is a dermatological disorder that can be more commonly seen in adolescents as well as younger patients. The pediatric acne is classified according to the age groups as neonatal acne, infantile acne, mid-childhood acne, and prepubertal acne. The presentation, pathogenesis, differential diagnosis, and treatment of the disease vary in each age group. Early diagnosis is important to prevent the scar formation and determine the underlying abnormalities.

Keywords: neonatal acne, infantile acne, mid-childhood acne, prepubertal acne

1. Introduction
Acne is one of the most common diseases in dermatology practice. Although acne has been known as a disease of the adolescents, it is also observed during the neonatal, infantile, mid-childhood, and prepubertal period. The severity of clinical findings varies mild to moderate in neonates but it could be more severe in different age groups. While the disease usually recovers spontaneously, in some severe scar formation cases, treatment should be needed. The treatment of acne is debate in these age groups, because of the possible adverse effects of the medications. Pediatric acne becomes a greater issue because it has a wide spectrum of differential diagnosis and could be associated with underlying systemic abnormalities [1–3].
2. Classification of pediatric acne

2.1. Neonatal acne

2.1.1. Presentation and pathogenesis

Acne developing in newborns at birth or within 4-6 weeks immediately after birth is called neonatal acne [1]. It is more frequently seen in newborn boys than in girls [2]. The incidence of neonatal acne diagnosed based on the presence of comedone lesions is approximately 20% in newborns [3].

Although the etiopathogenesis is not exactly known, there are debates as to whether they are true acne or not [4]. A positive family history shows that there is role of genetic factors [2]. Sebaceous glands stimulated by maternal and neonatal androgens, increased seborrhea and Malassezia species are also regarded to be responsible from etiology [5]. In addition, there are findings that demonstrate the importance of maternal effects on newborn sebaceous glands. Maternal androgens stimulate sebaceous glands by transplacental transmission instead of transmission by maternal milk [6]. Sebum secreted in large amounts during the neonatal period decreases over time and the sizes of the sebaceous glands gradually decrease towards the end of the sixth month [2]. In particular, the role of enlargement in the zona reticularis of the fetal adrenal gland and the resulting increased production of β-hydroxysteroids have been emphasized. Increased β-hydroxysteroids also cause enlargement in the sebaceous glands, thereby, increasing sebum production. Additionally, β-hydroxysteroids secreted from the neonatal adrenal glands cause the sebaceous glands to become more sensitive to hormones in the future [3]. Luteinizing hormone and testosterone are high in neonatal boys between the sixth and twelfth months. Adrenal androgens are responsible for neonatal acne in both newborn boys and girls. The presence of increased testicular androgens in males confirms why this disease is more frequently seen in boys [2, 3].

Neonatal acne is characterized by inflammatory lesions, such as papules and pustules, in addition to open and closed comedones, and rarely by nodules and cysts [1, 3]. It is most commonly seen in the cheeks and then in the forehead and less frequently in the neck and truncal region [3]. Neonatal acne, which is characterized by self-limiting mild symptoms, rarely continues to the ninth to twelfth months and can transform to infantile acne. In the majority of the patients, there is no underlying disease. Following a detailed history and physical examination, endocrinological abnormalities should be further investigated in the presence of signs of virilization or other abnormal findings [1, 4].

Acneiform eruptions and infectious and noninfectious diseases, which can be sometimes seen during the neonatal period, are involved in the differential diagnosis. In the differential diagnosis, acne venenata infantum, acneiform drug reactions, chloracne, bacterial (Staphylococcus aureus, Listeria monocytogenes, beta hemolytic group B streptococcus), viral (Herpes simplex, Varicella zoster, cytomegalovirus), fungal (candidiasis, pityrosporum folliculitis), and parasitic (scabies) infections as infectious causes and erythema toxicum neonatorum, infantile acropustulosis, milia, sebaceous gland hyperplasia, transient neonatal pustular melanosis, and pustular miliaria as noninfectious causes are often considered [5].
2.1.2. Treatment

As neonatal acne is a mild and transient condition, it recovers spontaneously within four weeks and three months without scar formation. Rarely, it can persist up to six to twelve months [5]. Topical agents are often beneficial for treatment. The gel, lotion, and solution forms of topical antibiotics containing erythromycin and clindamycin and topical benzoyl peroxide can be used for inflammatory lesions and topical azelaic acid (20% cream) and topical retinoids (tretinoin 0.025-0.05% cream) can be used for comedonal lesions [2, 4]. If systemic treatment is required, an oral antibiotic such as erythromycin should be preferred [7].

The clinical characteristics of neonatal acne are summarized in Table 1.

| Age at onset | Birth–6 weeks |
|--------------|---------------|
| Clinical presentation | Comedones, inflammatory papules and pustules, nodules, scarring |
| Differential diagnosis | Neonatal cephalic pustulosis, bacterial-viral-fungal infections, erythema toxicum neonatorum, infantile acropustulosis, milia, sebaceous gland hyperplasia, transient neonatal pustular melanosis, pustular miliaria, chloracne, acne venenata infantum, acneiform drug eruptions |
| Treatment | Recovers spontaneously without scar formationTopical azelaic acid, topical retinoids, topical antibioticOral antibiotic (erythromycin) |

Table 1. Neonatal acne.

2.1.3. Neonatal cephalic pustulosis

Neonatal cephalic pustulosis (NCP) is characterized by mild inflammatory papulopustular lesions and is differentiated from neonatal acne by the absence of comedones [1, 8]. In a study including 104 patients, the prevalence of NCP was approximately 25% in neonates [9]. It is thought to be due to the development of lipophilic yeasts in predisposed newborns who have increased sebum production. It has been demonstrated that Malassezia species, in particular, have a role in the etiopathogenesis of NCP [10, 11]. At birth, Malassezia colonization develops, depending on environmental factors, maternal contact, and the characteristics of newborn skin; it gradually increases within the first months of extrauterine life. In particular, *Malassezia sympodialis* and *Malassezia globosa* have a high prevalence. These fungi, which are found in the normal skin flora of infants, likely lead to follicular occlusion in predisposed infants who have increased sebum production. This, in turn, causes acneiform eruptions [8, 10, 12, 13]. However, the presence of negative mycological data in some NCP cases and the absence of NCP development in some culture-positive newborns lead us to believe that different factors also have an effect [1, 5]. There is a debate as to whether it is a hypersensitivity reaction developing against yeast or not [1]. In general, it is characterized by mild, transient lesions in the cheeks, chin, and forehead regions, which restrict themselves within a few weeks. As it is a self-limiting lesion, it does not usually require treatment. However, if needed, topical 2% ketoconazole cream twice daily for 1 week is an appropriate treatment method [4, 8, 14].
2.2. Infantile acne

2.2.1. Presentation and pathogenesis

Infantile acne is a less common occurrence, compared to neonatal acne and it is observed between the first and twelfth months of extrauterine life. However, it can also develop in later periods, such as the 14th and 16th months [4, 15]. Infantile acne is more diffuse, inflamed, and persistent [3]. Similar to neonatal acne, infantile acne is also more common in males [2, 4]. Lesions are typically characterized by open and closed comedones, inflammatory papules and pustules, nodules and less commonly by scar forming cysts [1, 2, 3]. Infantile acne is most frequently seen on cheeks and less commonly seen on the chest and back (Figure 1) [1, 2]. Acne conglobata, which has primarily facial involvement and is clinically similar to the adult form, is rarely seen [2]. Infantile acne, particularly conglobate infantile acne, may be associated with severe acne, which is seen during the adolescent period, and there is typically a positive family history of severe acne in these patients [16].

The causes of acne development during the infantile period are not so distinct. The presence of a positive family history emphasizes the role of genetic factors [8]. The general opinion tends toward the presence of sensitivity to the circulating adrenal and gonadal androgens. The release of adrenal androgens decreases close to age 1 and remains silent until the ages of 6-8. Zona reticularis which is the androgen-secreting part of fetal adrenal gland is large in both girls and boys and it gradually gets smaller beginning at age 1, during childhood period [8, 15]. It is thought that high levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) secreted as a result of the continuation of fetal adrenal gland function after the neonatal period causes acne development by stimulating the sebaceous

Figure 1. Infantile acne; an 8-month-old girl presented with closed comedones and inflammatory papules and pustules on her cheeks.
glands [4, 8]. While there are high amounts of luteinizing hormone (LH) and testicular androgen production until age one in boys, indeed, there is no testicular androgen production between age one and adrenarche. However, in girls, testosterone levels rapidly decrease at birth or within the first two weeks after birth. Thus, this situation explains why acne is more commonly seen in males [4, 8].

Most infantile acne is not associated with an underlying endocrinological abnormality. However, if the lesions are persistent, severe, and unresponsive to treatment, or if there is a finding of hyperandrogenism in the physical examination of the infant (pubic hair, cliteromegaly, hirsutism, alopecia, accelerated growth, etc.), additional laboratory investigations for underlying abnormalities should be performed [2, 7, 15]. Measurements of bone age, serological tests such as follicle-stimulating hormone (FSH), LH, free and total testosterone, DHEA, DHEAS, 17β-hydroxyprogesterone, prolactin, and adrenocorticotropic hormone (ACTH) stimulation test should be performed [2, 4]. In rapidly developing infantile acne, attention should be given to virilizing tumors [17]. If the tests reveal an abnormality, the infant should be referred to pediatric endocrinology.

In the differential diagnosis, acneiform eruptions developing due to the exposure are present. Acne venenata infantum or pomade acne can be seen due to comedogenic skin care product forms such as pomades, creams, ointments, and oil form that are used by the parents; corticosteroid-induced acne is seen in the perioral, periocular, and infranasal areas due to topical, oral, and inhaler corticosteroids; chloracne is seen in the centrofacial region due to accidental exposure to chlorinated aromatic hydrocarbons. In addition to these conditions, neonatal acne, perioral dermatitis, milia, and miliaria should be also considered in the differential diagnosis [4, 8].

2.2.2. Treatment

The course of the disease is variable. While the lesions disappear after one to two years in certain patients, they usually persist and most of the lesions recover after the age of four to five years. Less frequently, they can be active until puberty [3].

Parents of the patient with infantile acne should be warned about the fact that the disease can be persistent and severe acne can relapse during puberty [3]. The treatment of infantile acne is similar to the acne treatment in different age groups. Treatment varies according to the severity of the disease. In mild acne where comedone lesions are dominant, topical retinoids (tretinoin, adapalene) and/or the combination of topical benzoyl peroxide and topical antibiotic (erythromycin) can be used [5, 7, 18, 19]. Oral antibiotics can be used in more inflammatory lesions which are associated with papules, pustules, and nodules. The first choice, erythromycin, can be given in a dose of 125-250 mg, twice daily in this age group; if propionibacterium acne is resistant to erythromycin, trimethoprim 100 mg could be given twice daily [2]. It is necessary to avoid oral tetracycline before age 8, as it could cause damage to the teeth and bones. Intrallesional low dose triamcinolone acetonide (2.5 mg/mL), cryotherapy, and short-term topical corticosteroid therapy are options for acne associated with deep nodules and cysts [3, 18, 20]. Oral isotretinoin can be used, if there is no response or if there is scar formation [18, 21, 22]. Oral isotretinoin is approved by the Food and Drug Administration for
patients aged 12 and above in the treatment of nodulocystic acne [23]. In the literature, its use in children aged below five, at a dose of 0.36-2 mg/kg/day for 4-6 months, has been found to be effective; however, scar tissue occasionally remains [8, 22]. The optimal cumulative dose of isotretinoin during the infancy is unknown. Its use in young children is slightly more difficult, since it is found in soft gelatin capsules and inactivated by light and oxygen [21]. Thus, it should be opened under dim light and the daily recommended dose should be divided twice daily, by adding to food, such as butter, yogurt, a bread slice with jam, or milk. However, in this way, there is the possibility of inactivation or not taking the drug in recommended doses. Therefore, the capsule can be frozen in a viscous texture and cut in the required doses and given with a delicious food such as a candy bar [18, 21, 22]. This method prevents the wasting of the drug and also facilitates its use by decreasing the poor taste of the drug. Patients should be carefully followed for possible side effects. The most common side effect is dryness of the mucous membranes and the skin [4]. As it may lead to changes in blood counts, liver functions, cholesterol, triglyceride levels, adverse skeletal effects such as calcification of ligaments and tendons, cortical hyperostosis, periosteal thickening, premature epiphyseal closure, decalcification, and possible osteoporosis, laboratory evaluations, and skeletal growth should be followed on regular intervals [8, 21, 24].

The clinical characteristics of infantile acne are summarized in Table 2.

| Age at onset | 6 weeks–12 months |
|--------------|------------------|
| Clinical presentation | Comedones, inflammatory papules and pustules, nodules, less commonly by scar forming cysts, acne conglobata |
| Differential diagnosis | Acne venenata infantum/pomade acne, corticosteroid induced acne, chloracne, neonatal acne, perioral dermatitis, milia, miliaria |
| Treatment | Topical retinoids, topical benzoyl peroxide, topical antibiotic (erythromycin)Oral antibiotic (erythromycin, trimethoprim sulfamethoxazole)Intralesional low dose triamcinolone acetonide, cryotherapy; short-term topical corticosteroid therapy for nodules and cystsOral isotretinoin for scar formation lesions |

Table 2. Infantile acne.

2.3. Mid-childhood acne

2.3.1. Presentation and pathogenesis

Mid-childhood acne is observed between the 1 and 7 years of life [14]. Acne is quite rare during this period. The children in this age group do not secrete significant amounts of adrenal or gonadal androgens. Androgen secretion of adrenals often disappears after the first year of life until age 7 (adrenarche). Then, zona reticularis regains function. Therefore, hyperandrogenism should be investigated at the time of diagnosis [6, 8, 25].

Lesions are characterized by mixed comedones and inflammatory papules and pustules of the face, chest, and back [1].
In addition to premature adrenarche, which is a completely benign event, more severe conditions such as congenital adrenal hyperplasia (CAH), gonadal and adrenal tumors, Cushing’s syndrome, central precocious puberty, and exogenous androgen absorption should be excluded [2, 7, 15]. A careful physical examination should be done for the growth chart and the presence of findings related to hormonal abnormality. The bone age could be measured by radiological examination of the left hand or wrist [1, 2]. Laboratory tests such as serum total and free testosterone, DHEA, DHEAS, 17 alpha hydroxyprogesterone, FSH, LH, and prolactin levels should be measured to evaluate hormonal abnormalities [2]. If any abnormality is detected, it should be referred to pediatric endocrinology.

Inflamed keratosis pilaris, which is seen in the cheeks in atopic people, keratin cysts (miliaria), demodicosis, molluscum contagiosum, verruca plana, idiopathic facial aseptic granuloma, pseudoacne of the nasal crease, perioral dermatitis, and angiofibroma should be considered in the differential diagnosis of mid-childhood acne [7, 15, 26, 27]. In the literature, dactinomycin-induced acne has been reported in this age group [28].

2.3.2. Treatment

Its treatment depends on the underlying endocrinological abnormality. However, if necessary, topical treatments and oral antibiotics are similar to infantile acne [2, 8].

The clinical characteristics of mid-childhood acne are summarized in Table 3.

| Age at onset | 1–7 years |
|--------------|-----------|
| Clinical presentation | Comedones, inflammatory papules and pustules |
| Differential diagnosis | Inflamed keratosis pilaris, keratin cysts, demodicosis, molluscum contagiosum, verruca plana, idiopathic facial aseptic granuloma, perioral dermatitis, angiofibroma |
| Treatment | Depends on the underlying abnormalityTopical retinoids, topical benzoyl peroxide, topical antibiotic (erythromycin)Oral antibiotic (erythromycin, trimethoprim)Oral isotretinoin |

Table 3. Mid-childhood acne.

2.4. Prepubertal acne

2.4.1. Presentation and pathogenesis

Acne, which is observed between the ages of 7 and 11, is called prepubertal acne and its incidence has increased in recent years [15]. Contrary to expectations, acne can occur prior to pubertal signs. There is a genetic predisposition in these patients. An increased early-onset acne can be an initial finding of pubertal development rather than age [2]. Prepubertal acne is a consequence of normal adrenarche, which develops depending on adrenal gland maturation [7]. Acne development in premenarche girls has been reported as 61-71.3% [29, 30]. The most common presentation is comedonal lesions in the center region of the forehead. Inflammatory papules and pustules can be seen in the central of the face and sometimes in the ear concha,
chest, and back [1]. Advancing pubertal maturation was found to be correlated with the prevalence and severity of acne in both boys and girls [29, 31]. There are two components of pubertal development. The first component is adrenarche, which is the initiation of androgen synthesis (DHEA, DHEAS) together with the maturation of the adrenal gland at the age of 6-7 years in girls and at the age of 7-8 years in boys. DHEA and DHEAS lead to the development of seborrhea, odor, terminal and sexual hair, and acne. Excessive androgen production could be related to adrenal hyperandrogenism, congenital adrenal hyperplasia, Cushing’s disease, 21-hydroxylase deficiency, and androgen-secreting tumors. Furthermore, true puberty, the second component, is the maturation of the ovary and testis under the effect of the hypothalamo-pituitary-adrenal (HPA) axis. Androgen secretion from the gonads is low during this period of life. Excess ovarian androgens can be due to benign and malignant tumors; however, they are most frequently associated with polycystic ovary syndrome (PCOS) [2, 5, 7].

In a 5-year cohort study performed on girls, acne lesions increased with age and maturation was reported. The most common type of lesions was comedone. On the other hand, no ethnic differences were observed. The study revealed that the girls who had severe acne had more comedone and inflammatory lesions beginning from age 10 and 2.5 years before menarche and they had earlier menarche. High levels of serum DHEAS, free and total testosterone suggest that it could be an initiator of severe long-term disease [32].

In general, there is no need to further research prepubertal acne. If there is persistent acne that is unresponsive to treatment or findings suggesting androgen excess are detected, possible endocrinological abnormalities should be suspected. Tanner stages demonstrating pubertal development should be measured, a hand film should be taken for bone age, and serum-free and total testosterone, DHEAS levels and ratio of LH to FSH should be measured [8, 15, 25, 33].

Its differential diagnosis is similar to mid-childhood acne. In addition, the side effects of drugs such as corticosteroids and anticonvulsants, prepubertal hidradenitis suppurativa, adenoma sebaceum, keratosis pilaris, and inflamed keratin cysts should be considered in the differential diagnosis [2, 34–36].

2.4.2. Treatment

Nonetheless, data related to acne medications during the preadolescent period are limited. Most of the acne drugs are approved for age 12 and above. Its treatment is similar to infantile and mid-childhood acne. Topical retinoids (tretinoin 0.04% microsphere gel), benzoyl peroxide, and antibiotics can be used in mild to moderate comedonal and inflammatory acne. Oral antibiotics and oral isotretinoin may also be required in more severe scar forming lesions. As an oral antibiotic, erythromycin and its derivatives, trimethoprim, and cephalexin should be preferred. Tetracycline and its derivatives should be avoided, as these agents may produce dental enamel staining. Oral contraceptives or antiandrogens such as spironolactone can be used for PCOS and low-dose corticosteroids can be used for CAH. However, oral contraceptives should be used carefully due to the risk of premature epiphyseal closure [2, 5, 37].

The clinical characteristics of prepubertal acne are summarized in Table 4.
### Table 4. Prepubertal acne.

| Age at onset | 7–11 years |
|--------------|------------|
| Clinical presentation | Comedones, inflammatory papules and pustules, nodules, cysts |
| Differential diagnosis | Drug induced acne, prepubertal hidradenitis suppurativa, adenoma sebaceum, keratosis pilaris, inflamed keratin cysts, demodicosis, verruca plana |
| Treatment | Topical retinoids, topical antibiotics, topical benzoyl peroxide, oral antibiotics (erythromycin, trimethoprim, cephalexin), oral isotretinoin, oral contraceptives, antiandrogens, low dose corticosteroids |

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