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Neonatal and infantile acne – etiopathogenesis, clinical presentation and treatment possibilities

Trądzik noworodkowy i niemowlęcy – etiopatogeneza, obraz kliniczny oraz możliwości terapeutyczne

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Keywords

acne vulgaris, infant and newborn diseases, dermatologic agents, isotretinoin

Słowa kluczowe

trądzik pospolity, choroby niemowląt i noworodków, leki dermatologiczne, izotretynoina

Conflict of interest Konflikt interesów

None

Brak konfliktu interesów

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S u m m a r y

Neonatal and infantile acne are rare pediatric conditions. Compared to other types of acne there is a relative paucity of data on their pathogenesis and treatment. Current recommendations are mostly based on retrospective studies and case series. Androgen imbalance caused by maternal steroids in neonatal cases and endogenous secretion in infants is believed to be the primary cause of these forms of pediatric acne. Extensive workup for underlying endocrine causes is indicated in patients with symptoms of virilization, precocious puberty or growth disorders.

Neonatal acne (presenting at less than 4-6 weeks after birth) is usually a benign condition which resolves spontaneously and requires no treatment. However, differential diagnoses must include other acne-mimicking diseases e.g. neonatal cephalic pustulosis. Infantile acne on the other hand may have scarring potential and may require treatment with typical anti-acne drugs. Except for tetracyclines which are strongly contraindicated in pediatric patients almost all other medications including isotretinoin have been used with good effects.

This review focuses on the pathogenesis, clinical presentation and therapeutic possibilities of early childhood acne.

S t r e s z c z e n i e

Trądzik noworodkowy i dziecięcy są stosunkowo rzadkimi chorobami wieku dziecięcego. W porównaniu z innymi rodzajami trądziku dysponujemy ograniczonymi danymi naukowymi dotyczącymi ich patogenezy i leczenia. Aktualne rekomendacje opierają się przede wszystkim na badaniach retrospektywnych i opisach serii przypadków. Uważa się, że przyczyną trądziku dziecięcego są zaburzenia równowagi hormonalnej wywołane androgennymi steroidami pochodzenia matczynego u noworodków i wydzielanymi endogennie u niemowląt. W przypadku współwystępowania trądziku z objawami wirylizacji, przedwczesnego dojrzewania płciowego lub zaburzeniami wzrostu konieczna jest pilna diagnostyka w kierunku możliwych poważniejszych zaburzeń endokrynologicznych.

Trądzik noworodkowy (występujący w czasie krótszym niż 4-6 tygodni po urodzeniu) przebiega zwykle łagodnie, ustępuje samoistnie i nie wymaga leczenia. Diagnostyka różnicowa musi jednak obejmować inne choroby naśladujące trądzik, np. noworodkową krostkowicę głowy. Natomiast trądzik niemowlęcy może mieć ciężki przebieg, z pozostawieniem blizn, i wymaga leczenia typowymi lekami przeciwtrądzikowymi. Z wyjątkiem tetracyklin, które są przeciwwskazane u dzieci, prawie wszystkie inne leki, w tym izotretynoina, były stosowane z dobrymi efektami.

Niniejsza praca skupia się na patogenezy, objawach klinicznych i możliwościach terapeutycznych trądziku wczesnodziecięcego.

INTRODUCTION

Acne vulgaris occurs in 79-95% of adolescents and young adults (1). Often, however, it develops in infants and children before adolescence. Under certain circumstances, especially when the symptoms of premature puberty or virilization coexist, it must induce diagnostic work-up towards underlying endocrine disorders (2). Treatment of acne in neonates and infants should be adjusted to the severity of acne. Beside tetracyclines, which are absolutely contraindicated in this age group, medications used should be adapted to the type of acne lesions. Most anti-acne drugs are not registered in children under 12 years of age. According to pediatric acne treatment consensus they can be used in infants, but with extreme caution.

Neonatal and infantile acne are part of the spectrum of pediatric acne. Table 1 presents the current distinction between the five types of pediatric acne (3). This division is based on the child's age at the development of the first acne lesions.

Tab. 1. Division of pediatric acne according to age at onset

Neonatal acne	During first 6 weeks of life
Infantile acne	Between 6 weeks and 12 months
Mid-childhood acne	Between 1 and 6 years
Prepubertal acne	Between 7 and 12 years or until first menstruation in girls
Juvenile acne	Between 12 and 19 years

NEONATAL ACNE

Neonatal acne occurs in the first 6 weeks of life and affects about 20% of newborns (4). It usually manifests with small, closed comedones located on the forehead, nose and cheeks with frequently co-existing sebaceous gland hyperplasia (5).

The pathomechanism of acne formation in this age group has not been fully explained. It is believed that it is caused by the increased production of sebum in enlarged sebaceous glands under the influence of maternal androgens delivered through placenta and beta-hydroxysteroids produced in excess by the newborn's adrenal cortex (dehydroepiandrosterone – DHEA, dehydroepiandrosterone sulfate – DHEA-S). Additionally, some of the affected male newborns may have elevated levels of testicular androgens, produced under the influence of luteinizing hormone (LH), levels of which in these children may reach puberty values (7). LH stimulates the synthesis of testosterone which leads to increased seborrhoea. This phenomenon may explain increased incidence of neonatal acne in boys (7, 8). Neonatal acne subsides spontaneously within 1 to 3 months and does not require pharmacological treatment (9).

Differential diagnosis should include viral, bacterial and fungal infections, neonatal milia, sebaceous gland hyperplasia, neonatal pustular melanosis and neonatal toxic erythema (10). Particularly frequently observed is the occurrence of neonatal cephalic pustulosis. In this

case, skin lesions are acne-like without the presence of comedones. It is most likely caused by *Malassezia* yeasts colonizing the skin (11). In most cases, treatment is not required (12). In patients with severe changes, 2% ketoconazole creams (13) can be used.

INFANTILE ACNE

Infantile acne occurs primarily between 6 weeks and 12 months of age and similarly to neonatal acne male predominance is observed. Skin changes such as comedones and inflammatory lesions (papules, pustules, cysts) are located mainly on the cheeks. However, the lesions may have more severe character and may be more numerous in comparison with acne in newborns (14).

In most children acne remits before 4-5 years of age and only rarely persists until adolescence (15). Contrary to the neonatal acne, this form of acne can leave scars, which prompts early treatment, especially in more severe cases (14). Conglobate acne characterized by burrowing and interconnecting abscesses and irregular scars (both keloidal and atrophic) has been described in this age group but is very rare (16).

As with the neonatal acne, it is believed that the infantile acne is induced by androgens secreted by the adrenal cortex in both sexes (7). Elevated values of DHEA secreted by the adrenal cortex are observed up to 12 months of age. After this period there is a decrease in the secretion of DHEA, which results in a gradual remission of skin lesions (8). Higher prevalence of infantile acne in boys can also be explained by the increased secretion of LH which stimulates testicular androgen synthesis. This process is probably a result of the immaturity of the hormonal feedback mechanism between the gonads and the pituitary gland (14, 17).

Propionibacterium acnes (18) also plays an important role in the etiopathogenesis of acne. These are commensal gram-positive, lipophilic, anaerobic microbes, colonizing seborrhoeic areas of the skin. The composition of seborrhoeic microbiome is subject to significant changes during human life. Infant skin is dominated by *Firmicutes* phylum and their number is significantly higher than *Actinobacteria*, which include *Propionibacterium* genus (19). During puberty the sebaceous gland microbiome shifts towards dominance of *Propionibacterium* and *Corynebacterium* (20). Increased seborrhoea is closely followed by the increase in the quantity of *Propionibacterium acnes*. It has been demonstrated that in children with acne the process of skin colonization by *Propionibacterium acnes* is much faster than in children without acne (21). It is believed that these bacteria contribute to the development of acne (comedones, inflammatory lesions) by stimulating keratinocyte proliferation and the synthesis of proinflammatory factors such as interleukin 8 (22).

Infantile acne rarely coexists with endocrine disorders and only in the presence of clear symptoms of virilization or premature puberty does require extensive diagnostics. Detailed physical examination is essential

with particular attention to the assessment of developmental parameters such as height, weight, growth curve, testicles, mammary glands, presence of pubic hair, hirsutism, clitoral hypertrophy or increased muscle mass. In the case of any abnormalities bone age assessment and initial hormonal tests (FSH, LH, testosterone, dehydroepiandrosterone sulphate) should be obtained followed by a prompt referral to a pediatric endocrinologist (3).

Harde et al. have described the case of a 23-month-old boy with acne since the early infancy. They found excessive growth (99.6 percentile) corresponding to a child twice the age and enlarged genitals with pubic hair. The development of acne preceded these symptoms by several months. After detailed examination, he was diagnosed with congenital adrenal hyperplasia caused by 11-beta-hydroxylase deficiency. It caused a decrease in the synthesis of corticosteroids and an overproduction of androgens due to the constant stimulation of the adrenal cortex via pituitary ACTH (23).

Androgen-secreting tumors have also been reported as a causative factor in infantile acne. Mann et al. have described a case of a boy with androgen-secreting adrenal tumor. Importantly, beside acne the child also demonstrated features of virilization and excessive growth, which underlines the importance of a thorough physical examination in children with acne. It should be noted, however, that such tumors are very rare and account for only 0.02% of childhood cancers (24).

Unfortunately, infantile acne predisposes to the development of severe forms of acne in later life (7). For this reason effective acne treatment should be quickly implemented in adolescent patients with a personal history of infantile acne in order to prevent the occurrence of severe, scarring forms of the disease.

Between 1 and 7 years of age acne is extremely rare. The adrenal cortex produces very small quantities of androgens during early prepubertal period. It is only around the age of 7 that the reticular layer of this organ begins to produce gradually increasing amounts of sex steroids (25). The appearance of acne between 1 and 7 years of age, especially with concurrent signs of premature puberty must prompt the exclusion of ovarian and testicular pathology, congenital adrenal hyperplasia, Cushing's syndrome and rare but possibly life-threatening androgen-secreting tumors.

TREATMENT

The treatment of acne in infants is a significant problem for dermatologists, as topical and general medications are not registered for use in this age group. In addition, due to the polymorphism of acne lesions (comedones, inflammatory lesions) and sometimes the occurrence of severe forms of acne several drugs should be used simultaneously for treatment to be effective. This raises concerns about the risk of drug interactions, local or systemic complications, or developmental disorders.

For infants, the simplest formulas with the lowest possible side effects should be used. However, they

must be adapted to the morphology of skin lesions and the severity of acne.

Guidelines for treating acne in children up to 12 years of age were published in 2013 in "Pediatrics". They point out that, in the case of infants, topical medications such as benzoyl peroxide, retinoids, antibiotics and combined preparations are not contraindicated and can be safely used (3). In infants as well as in older children, the use of antibiotics in monotherapy should be avoided due to the increasing antibiotic resistance (27).

Side effects which are most often present in the form of local skin irritations should be managed by decreasing the frequency of application and by moistening the skin with non-comedogenic preparations (17).

Local treatment may be insufficient in severe cases of acne during infancy presenting with numerous inflammatory lesions including purulent cysts. Consideration should be given to the employment of systemic therapy. Tetracyclines, widely used in adults and children over 12 years of age, are contraindicated in infants because they interfere with the development of teeth (28). Erythromycin is an effective therapeutic option at the dose of 125 mg twice daily orally (17). Among other antibiotics that can be used in infants with severe inflammatory acne are amoxicillin, cefalexin, trimetoprin-sulfometaxazole and azithromycin (29). These antibiotics are also used in many infectious diseases and due to the increasing antibiotic resistance and possible side effects should only be used as second line drugs.

If there is no improvement after oral antibiotics or the acne is very severe with scarring oral isotretinoin can be used with due caution (4). During the treatment with isotretinoin, the child requires constant medical supervision and monitoring of laboratory parameters, i.e. blood count with smear, lipidogram with particular emphasis on triglycerides and hepatic enzymes, renal function and glucose (7). One should begin with a dose of 0.5 mg/kg per day to prevent an exacerbation at the beginning of therapy. The dose can then be titrated up to 1 mg/kg (3). In the case of a typical dosage used in the treatment of acne there is no increased risk of bone demineralization or fractures (30, 31). Few cases of the premature closure of lower extremity growth plates caused by isotretinoin and other vitamin A analogues were reported in the literature (32).

Long term treatment with high-dose vitamin A analogues, commonly administered in keratinisation disorders, increases the risk of extraspinal hyperostosis. This phenomenon, however, with relatively low dosage of retinoids and short therapy is very rarely observed in acne (33).

Many cases of the effective treatment of severe forms of acne in infants using isotretinoin have been described in the literature. Torrelo et al. have reported the case of a 10-month-old boy with a severe scarring on his face. After ineffective treatment with erythromycin, oral treatment with isotretinoin 1 mg/kg resulted

in a complete remission of skin lesions. During the treatment, no side effects were observed. Laboratory parameters were also within normal range (34). Miller et al. in their retrospective study described cases of 6 boys with severe acne and high risk of scarring effectively and safely treated with oral isotretinoin. The average age of children was 6.2 months. No significant adverse reactions have occurred, neither during the treatment nor in the follow-up (35).

We should also mention the importance of proper education of parents. This is very important in terms of the adherence to medical advice, knowledge of possible complications and avoidance of substances that may induce the so-called cosmetic acne in infants. In this case, parents should beware of cosmetics in the form of essential oils or greasy ointments. Additionally, it should be reminded that exposure to toxic agents

such as halides or aromatic hydrocarbons may also cause severe forms of acne in children.

CONCLUSIONS

1. Neonatal acne in most cases resolves spontaneously without leaving scars and does not require treatment. It is important to differentiate it from other skin diseases that occur during this period of life, especially neonatal pustulosis.
2. Infantile acne poses the risk of scarring and may require treatment, which in most cases is similar to that of adolescent acne.
3. Extensive endocrinological testing should be performed in cases of acne coexisting with other symptoms suggesting endocrine disorders such as virilization symptoms, premature puberty or growth disorders.

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received/otrzymano: 6.02.2018
accepted/zaakceptowano: 27.02.2018