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Advances in the Study of Risk Factors for Prepubertal Acne

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Abstract: Acne is a chronic inflammatory skin disease involving follicular sebaceous gland units, and there is no discussion of pre-pubertal acne in the risk factor reports of acne published in national journals. However, in our clinical work, we have seen an increase in the number of patients presenting to the clinic with pre-pubertal acne, which has a series of adverse physical and mental health effects on children who are undergoing rapid growth and development, leading to increased psychosocial stress and low self-esteem in these children. Therefore, this review will summarize the risk factors of prepubertal acne in light of the latest domestic and international research progress.

Pre-adolescent acne (acne) is a chronic inflammatory dermatologic condition involving the sebaceous glandular units of hair follicles that occurs in children between the ages of 7 and 12. It is a chronic inflammatory skin disease characterized by acne on the forehead and midface (rarely on the trunk), sebum production, and an increase in the number of sebaceous follicles[1], and is easily recurrent. As one of the most common diseases in dermatology outpatient clinics, acne that occurs before puberty is not fatal compared to other diseases, but because it often appears on the face, and the importance of appearance increases during this period, it can have an incalculable impact on the psychological and mental aspects of the patients who visit the clinic.

1. Epidemiological

Acne vulgaris is one of the most common chronic inflammatory skin diseases recognized by dermatologists, and its most prominent sites are found in areas with a high density of sebaceous gland distribution, such as the face, back, and chest. People of all ages and races around the world are susceptible to this disease. It has been investigated that it is most likely to occur in the pre-pubertal or pubertal periods, i.e., 7-12 and 12-18 years of age[2]. It is also no longer exclusive to adolescent boys and girls; the age of first occurrence of acne is constantly advancing, and the lower limit of its onset is no longer limited to 12 years of age. In an early study that included 365 female children (aged 9-10 years), it was found that 78% of them had acne lesions[3]. In a 3-year study in Korea, the prevalence of acne in children aged 7-12 years was 12.1%[4]. Usually, the incidence of acne is

proportional to age, peaking at 15-17 years old for girls and 17-19 years old for boys. With changes in living standards and dietary habits, the onset of puberty is common, and the age of onset of acne in females can be a little earlier than in males. The onset of prepubertal acne may precede other signs of pubertal maturation. Therefore, to rule out the presence of primary medical conditions such as polycystic ovary syndrome and precocious puberty in such patients, we perform a detailed and rigorous history and examination.

2. Pathogenesis

The current understanding of the pathogenesis of acne is that it is related to hormone-induced overproduction of lipids by sebaceous glands in a genetic context, abnormal keratinization of follicular sebaceous gland ducts, proliferation of follicular microorganisms such as Propionibacterium acnes, and inflammatory and immune responses, with androgen-induced increases in sebum production and secretion being considered to be the major pathophysiologic factors. Therefore, acne can be considered one of the typical representatives of androgen-mediated skin diseases.

Patients with pre-pubertal acne may produce high levels of adrenal or gonadal hormones, often referred to as the first signs of adrenal function, which usually occur around the age of 6-8 years. Based on this physiological phenomenon, the adrenal cortex produces increasing amounts of androgens. Androgens are important steroid hormones in the body and act by regulating the embryology of sebocytes as well as lipogenesis or sebum synthesis. As the body's androgen stores increase, sebum production increases in children, and the size of the sebaceous glands changes. In addition, the development of severe acne is closely related to the regulation of the androgen receptor.

In acne patients, the population of Propionibacterium acnes also appears to differ from the normal population. Propionibacterium acnes belongs to the group of rod-shaped Gram-positive bacilli that are the normal microbiota colonizing the skin. The presence of blocked follicular sebaceous gland units and sebum in acne patients provides a favorable anaerobic environment for the growth and reproduction of Propionibacterium acnes (P. acnes), enabling it to release large amounts of lipase and chemokines, which promotes acne formation and stimulates the organism (via inflammatory and keratin-forming cells) to produce further pro-inflammatory mediators and reactive oxygen species. In addition, Propionibacterium acnes hydrolyzes the triglycerides contained in sebum to free fatty acids, which in turn produces inflammatory lesions.

Precocious puberty usually occurs before the age of 8 years in girls and 9 years in boys. In prepubertal acne patients with precocious puberty, the onset of lesions may be related to the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which is paralleled by an increase in the sensitivity of the pituitary gland to respond to GnRH, and a concomitant increase in the secretion of gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In boys, LH stimulates the development of testicular interstitial cells and promotes their secretion of the androgen, and testosterone, and in girls, FSH promotes the development of ovarian follicles, which secrete estrogen and small amounts of androgens. Androgens gradually induce sebum production and increase its secretion, which eventually develops into acne.

3. Risk Factors for the Development of Prepubertal Acne

3.1. Internal Factor

3.1.1. Genetic Factor

The development of acne cannot be separated from the synergistic effect of multiple factors and

the dysregulation of multigene expression, and studies on the genetic aspects of acne vulgaris are currently being updated. In recent years, many researchers have explored the role of genetic factors in the pathogenesis of pre-pubertal acne, and a series of experimental data have demonstrated the association between genetic polymorphisms and the pathogenesis of acne, confirming that genes such as TNF-alpha, TNFR2, TLR2, IL-1alpha, CYP1A1, CYP17, and AR play an important role in acne pathogenesis and that some of them even have a direct relationship with the severity of acne. role, and some are even directly related to the severity of acne. The presence or absence of a history of acne in the immediate family (especially the mother) has been shown to have the greatest impact on the age of lesion onset, severity, and outcome of acne patients. In a series of reports on acne in Lithuanian adolescents, it was shown that a positive parental history of acne would have a very strong influence on the overall prevalence of acne in their children[5]. Patients with a positive family history had an earlier first appearance of lesions, more severe lesions, and a poorer prognosis after oral and topical medications than patients without a positive family history. The relationship between genetic factors and prepubertal acne is currently not very controversial among former researchers.

3.1.2. Endocrine Factors

Acne that occurs before puberty is mostly triggered by the first signs of adrenal function, but it may also appear as the first symptom in children with true precocious puberty, congenital adrenal hyperplasia, polycystic ovary syndrome, or rare androgenic tumors. For children who develop acne but show no other signs of puberty, a key pre-diagnostic step is to test their androgen levels, including testosterone, androstenedione, 17-hydroxyprogesterone, dehydroepiandrosterone, and dehydroepiandrosterone sulfate. Patients with excessive androgen production often experience a range of manifestations of acne vulgaris. Acne caused by endocrine diseases will have additional external manifestations on physical examination, including body odor, height and weight advancement compared to peers, breast development, and axillary and pubic hair [6]. Therefore, we must conduct a rigorous questioning and physical examination of patients with prepubertal acne to prevent other endocrine disorders from harming the patient.

3.1.3. Skin Type

Skin type, or skin texture, consists of four main categories: dry, normal, oily, and combination skin. Oily skin is characterized by enlarged facial skin pores, facial greasiness and higher oil production. Increased sebum production is a key factor interrelated with the development of acne, and it has been previously reported that acne-prone populations have higher levels of facial sebum than normal populations. The keratinization process of sebaceous gland ductal epithelial cells is also affected by changes in sebum composition, and their hyperkeratinization is closely related to the development of acne. Wang Rui[7]and others found that oily skin and combination skin had a higher prevalence of acne compared to other skin types. It has also been clinically observed that prepubertal children with oily skin and combination skin are more prone to acne. Excessive sebum secretion occurs due to an increase in androgen and IGF-1 activity, which increases sebum secretion, leading to blockage of hair follicles and the formation of lesions such as pimples, papules, and pustules.

3.2. External Factors

3.2.1. Dietary Factors

According to the currently available data, a variety of factors, either in combination or alternately, can influence the development of acne, with dietary factors being a hot topic of research in recent years. The onset of pre-pubertal acne is associated with a high-sugar diet, a spicy diet, and dairy

intake, whereas a Mediterranean diet, a ketogenic diet, and fish intake may be negatively associated with the development of acne. High-sugar and high-protein diets upregulate the insulin/ IGF-1 signaling pathway (IIS), which leads to uninhibited IGF-1 secretion, and also modulate the mammalian target of rapamycin complex (mTORC)1 signaling pathway, which leads to sebaceous gland hyperplasia, increased sebum content, insulin resistance, and increased BMI, which ultimately results in an increased risk rate for the development of acne. Milk and diets high in glycemic load may exacerbate acne by elevating serum IGF-1 levels. In a 1-week comparative experimental study of 8-year-old boys given meat and skimmed milk daily, insulin and IGF-1 levels were significantly increased in the milk group, but not in the meat group[8], suggesting that dairy products can increase the risk of acne in prepubertal children. Insulin and IGF-1 levels gradually increase with the intake of milk and a high-sugar diet, activating the mTORC1 signaling pathway, which ultimately leads to early menarche, weight gain, insulin resistance, and acne in females, and dietary interventions can lead to a reduction in the incidence of metabolic disorders in adulthood, such as diabetes mellitus, obesity cancer, and so on. Spicy foods have an irritating effect on the tiny arteries in the skin and the sebaceous glands of the hair follicles, prompting the sebaceous glands to secrete sebum, which triggers and exacerbates acne.

The Mediterranean diet and the ketogenic diet are similar in that they contain less sugar, carbohydrates, and sodium, and more cereals, and are low GL/GI diets. Low GL diets decrease the free androgen index and increase insulin growth factor-binding protein-3, and low GI and low GL diets decrease IGF-1 levels, which has a protective effect on the development of acne. Low GI and low GL diets also reduce IGF-1 levels, which is protective against acne development. Fish is high in Omega-3 fatty acids, which have been shown to reduce IGF-1 levels, which in turn reduces sebum production and ultimately follicle clogging, and inhibits the synthesis of inflammatory mediators (leukotriene B4), which reduces the incidence of inflammatory lesions in acne. An association between reduced fish intake and increased acne severity has also been reported, so it can now be assumed that fish intake is a protective factor in the development of acne.

3.2.2. Sleep Factors

Disruption of circadian rhythms is extremely harmful to the organism and can easily lead to a range of skin diseases. In prepubescent children, rapid physical growth and development, increased academic pressure, chronic late-night behavior, and insufficient hours of sleep may lead to imbalances in the circadian rhythm of the gut microbiota, which is characterized by changes in the composition and activity of the gut microbiota. This includes an increase in the abundance of pro-inflammatory bacteria and a decrease in specific anti-inflammatory bacteria in the gut, which in turn leads to a decrease in the body's immunity and metabolic function, causing the development of inflammatory skin diseases. Therefore, it can be assumed that circadian rhythm disruption is one of the predisposing factors for the development of pre-pubertal acne. Circadian rhythm disorders can also cause some flora colonized in the skin not to be properly adapted, especially Propionibacterium acnes, which can trigger or aggravate acne. Poor sleep habits can affect the activity of intestinal metabolites that regulate circadian rhythms, such as short-chain fatty acids and intestinal cocci and bacilli, leading to the development of acne.

3.2.3. Seasonal Factors

Follicular worms are mostly found in areas with high sebaceous gland production and are closely associated with the development of acne. Some studies have shown that the infection of Trichophyton rubrum varies greatly from season to season, with the rate of Trichophyton rubrum infection being higher in summer than in other seasons, followed by spring, and lowest in winter. Xiong Ying[9] and

others found that there is a relationship between the severity of acne vulgaris and seasonal changes. This is also consistent with our clinical observation that the number of prepubertal acne patients attending dermatology outpatient clinics is significantly higher in summer than in other seasons.

3.2.4. Personal Factor

Pre-adolescent children need a variety of nutrients, and if they have unbalanced nutritional ratios, a biased diet, or are sedentary and physically inactive, their body mass index (BMI) will be higher than normal, which also increases the potential risk of acne. Overweight/obese students have a higher prevalence of acne than underweight or normal-weight children. High BMI may be associated with high glycemic load and hyperandrogenemia, which affects sebum production, which in turn leads to hyperkeratosis of the follicles and the eventual development of acne. In addition to the above, there is still controversy as to whether smoking status affects the prevalence of acne, and the evidence is mixed as to whether smoking is a protective factor or a risk factor for acne. Some researchers have found smoking to be a risk factor for acne. However, other similar reports have shown that the prevalence of severe acne is significantly lower in frequent smokers than in non-smokers. Therefore, the potential relationship between acne and smoking and the mechanisms involved need to be thoroughly investigated.

3.2.5. Stressors and Psychological Factors

The age of 7-12 years is a critical period in the healthy development of the body and mind, as well as an important point in the transition to puberty when children are under great pressure from school and are prone to anxiety, irritability, and depression, which can lead to endocrine disruption and the emergence of acne. A large amount of literature found that stress and bad mood are closely related to the occurrence of acne. According to Zhao Yuxia[10], the disfiguring nature of acne can lead to abnormal emotions, which in turn can aggravate acne symptoms, leading to a vicious circle. Adverse emotional factors and the occurrence and development of acne are mutually causal and affect each other.

4. Discussions

The incidence of pre-pubertal acne is increasing year by year, and children are increasingly concerned about their "face", so it is important to explore the risk factors for its pathology for the early prevention and treatment of acne. After reviewing a large amount of literature, it was concluded that the risk factors for pre-pubertal acne are divided into two major parts: internal and external factors, but most of the pre-pubertal acne appearances are related to external factors. Among them, internal factors include genetic, endocrine, and skin type influences, while external factors are closely related to diet, sleep, season, personal, stress, and psychological factors. These risk factors can be effectively targeted for prevention, and health education can be provided to patients with pre-pubertal acne and their parents, thereby reducing the incidence of such disorders.

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