CLINICAL PARTICULARS AND THERAPEUTIC CHALLENGES IN PEDIATRIC PSORIASIS

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Summary

Psoriasis is a chronic recurrent inflammatory dermatosis with genetic and immunological determinism with onset in childhood in about one-third of cases. Although the clinical forms of childhood psoriasis are similar to those of adults, the lesions may differ in distribution, morphology, and onset manner. The positive diagnosis is established based on clinical criteria and histopathological examination. Childhood psoriasis is accompanied by many comorbidities such as obesity, high blood pressure, dyslipidemia, diabetes and juvenile rheumatoid arthritis, and the long-term psychological impact is more pronounced in children and adolescents compared to adults. The absence of treatment guidelines leads to difficult management of pediatric psoriasis, especially of refractory cases that require systemic therapy. The need for an international registry for reporting cases of childhood psoriasis and a standardized assessment of treatment effectiveness and adverse reactions is currently urgently needed. This paper reviews current concepts regarding epidemiology, clinical features, diagnosis, and therapeutic management in childhood psoriasis.

Keywords: *childhood psoriasis, clinical aspects, treatment, challenge.*

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Introduction

Psoriasis is a chronic immune-mediated inflammatory dermatosis, with genetic determinism and recurrent nature that affects the skin, nails and osteo-articular system [1]. Psoriasis vulgaris is clinically characterized by erythematous-papulosquamous plaques, with regular contour, well delimited, electively arranged on the extension faces of the limbs and on the scalp. The fluctuating evolution between the activity and remission episodes has a significant negative psycho-social impact. The disease has a systemic aspect considering the polymorphic psychological, metabolic, rheumatological and cardiovascular implications [2].

Psoriasis vulgaris accounts for about 5-6% of all dermatological diseases, affects both sexes equally, and its onset can occur at any age, from childhood to the eighth decade of life. Two peaks of onset age have been reported: one at 20-30 years and a second at 50-60 years. In about 75% of patients, the onset is before the age of 40, and in 35-50% before the age of 20. Women tend to develop the disease earlier than men, but the evolution is the same regardless of gender, with intermittent remissions [3, 4].

Pediatric psoriasis currently accounts for about one-third of the total number of cases of psoriasis. Statistical reports indicate that 40% of adults with psoriasis had symptoms in childhood, at least 30% of them earlier than 16 years. The prevalence of juvenile psoriasis in Europe is about 0.7%, with an increase from 0.37–0.55% in the age range 0-9 years to 1.01–1.37% in the age range 10-19 years. The onset in boys is usually between 6-10 years, and in girls between 10-14 years. The current

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incidence is estimated at 40.8 per 100,000 children and adolescents [5].

The clinical form in plaques is most common in children, followed by gout. Skin lesions are characterized by erythematous-squamous plaques, well defined, with recurrent chronic evolution and varying degrees of severity, from limited lesions to plaques spread throughout the skin [6].

Children diagnosed with psoriasis have numerous comorbidities such as obesity, diabetes, high blood pressure, rheumatoid arthritis, Crohn's disease and psychiatric disorders, compared to healthy subjects of the same age. Psoriasis in children and adolescents has a detrimental influence on social integration, family and school relationships, the psychological support being essential for these patients. For these psychological, social, and last but not least organic reasons, early diagnosis and appropriate therapeutic management are essential in the harmonious development and social integration of children and adolescents with psoriasis vulgaris [7, 8].

Etiopathogeny and risk factors

Genetic determinism and functional abnormalities of the immune system are the main etiopathogenic factors of clinically manifest infantile/juvenile psoriasis. Statistically, the involvement of family history in one third of the cases of pediatric psoriasis has been demonstrated, but numerous studies have shown the contribution of "trigger" factors in the onset or worsening of pediatric psoriasis. From this category, the psycho-emotional traumas from childhood and the infections of the upper respiratory tract are the "trigger" factors frequently involved in the etiopathogenesis of pediatric psoriasis.

Obesity frequently associated with endocrinological disorders in childhood is considered a trigger of "de novo" psoriasis, skin trauma can precipitate pre-existing psoriatic lesions, and the use of drugs (beta-blockers, lithium, antimalarials, nonsteroidal anti-inflammatory drugs) is a less common trigger of psoriasis in children compared to adults [9, 10].

Clinical particulars in pediatric psoriazis

The clinical subtypes of pediatric psoriasis are similar to those seen in adults, with some differences in the distribution, morphology and manner of onset of lesions. In childhood, typical erythematous-scaly plaques are smaller in size, tend to soak, and the scales are finer. The lesions are usually symmetrical and can develop on any area of the skin, but the preferred regions are the face and the flexion areas [11, 12].

Psoriasis in newborns, also called Napkin psoriasis, is a clinical form whose diagnosis is still controversial given the morphology of the lesions that mimic the rash of diaper rash. Napkin psoriasis is characterized by well-defined erythematous plaques, sometimes macerated or covered with fine scales, elevated in the diaper area, which affects the anogenital region, with a tendency to spread to the groin folds within 1-2 weeks. The classic treatment indicated in diaper rash is ineffective in this case. The frequency of anogenital localization decreases with age, and the lesions gradually take on the appearance of typical erythematous-squamous plaques. The main complication of this localization is superinfection with bacteria or fungi that appear in the context of skin cracking, especially in the groin area. The definite diagnosis of psoriasis in newborns remains a challenge, being established in most case over time, based on the evolution of the disease [13].

In older children and adolescents, the most common clinical appearance is plaque psoriasis (75% of cases). The cutaneous expression is of erythematous-papulosquamous plaques, well delimited, with regular contour, on a salmon-pink erythematous base, covered with pearly-white scales, plurilayered, non-adherent, with positive spermaceti and Auspitz signs according to the methodical grattage of Brocq. The lesions vary in size and are located mainly on the scalp, face, elbows, knees and extension faces of the limbs (Fig.1, Fig. 2). Scalp damage is often the first form of psoriasis in children [14].

Guttate psoriasis is the second most common type of psoriasis in children (28.9% of cases). It is defined as an acute papular rash that appears on the trunk about 2 weeks after a viral or bacterial

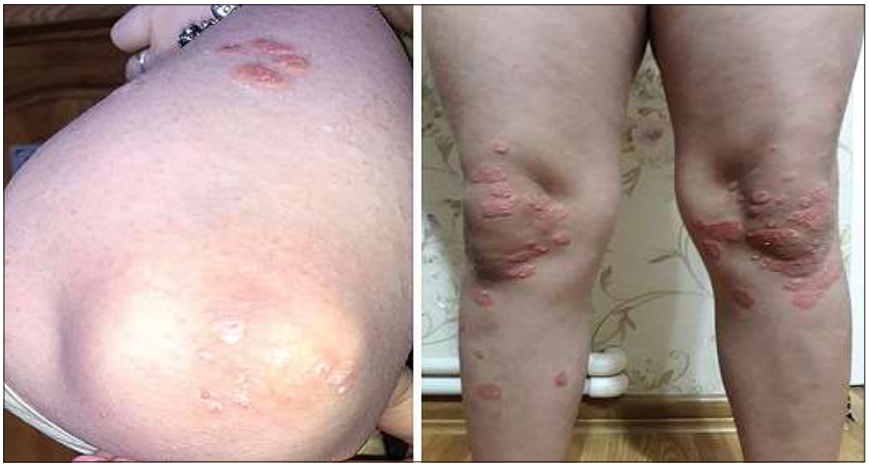

Figure 1. Childhood psoriasis - elbow and knee clinical expression

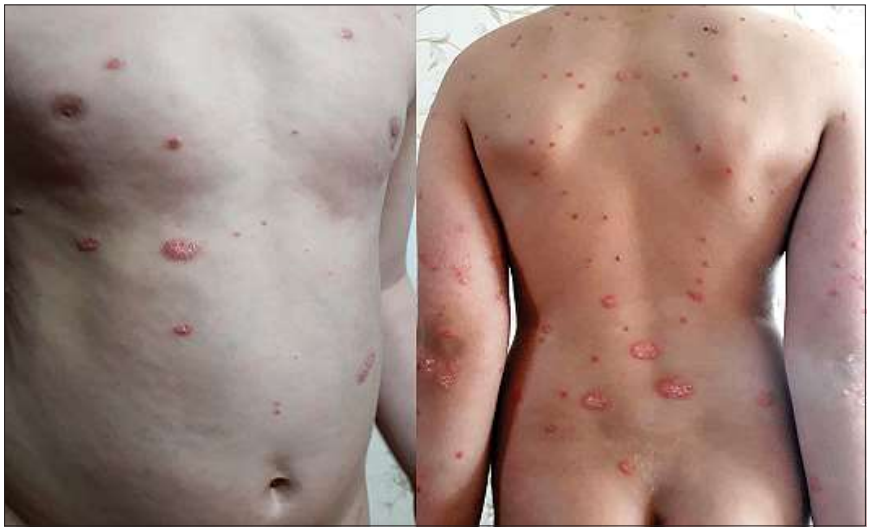

Figure 2. Infantile psoriasis - clinical expression antero-posterior thorax and lumbar area

infectious episode with β-hemolytic streptococcus. The guttate rash has a self-limiting character, it remits within 3-4 months from the onset. This way of onset through a guttate form involves a high risk of eventually developing a severe form of plaque psoriasis.

The pustular clinical form represents only 1.0–5.4% of cases of pediatric psoriasis.

In a minority of these patients, mutations in the interleukin-36 (IL-36) and IL-1 receptor antagonist genes were observed. Clinically it is characterized by sterile localized or generalized superficial pustules, sometimes accompanied by systemic manifestations such as fever, altered general condition, arthralgias, form called in the literature von Zumbusch. Although pustular psoriasis is more common in adults, the von Zumbusch and ring-shaped pustular form occur more frequently during childhood [15, 16].

Other less common clinical subtypes of pediatric psoriasis are inverse psoriasis, palmoplantar psoriasis, isolated facial psoriasis, linear psoriasis or erythrodermic psoriasis. Erythroderma occurs extremely rarely in children

and is considered a dermatological emergency given the severe hydroelectrolytic imbalances, the severe hypothermia and the risk of heart attack it associates [17].

Skin damage is accompanied by nail changes in about 40% of children with psoriasis, especially in males. These precede or coincide with the onset of skin lesions. The most common nail change is "pitting", followed by onycholysis, subungual hyperkeratosis, onychodystrophy and subungual hemorrhage. Juvenile psoriatic arthritis is an extracutaneous pathological condition associated with juvenile psoriasis. Prevalence data range from 1 to 10% due to the difficulty in diagnosing and classifying arthritis in this age group [18].

Therapeutic management of pediatric psoriasis

Pediatric psoriasis therapy is a challenge given a number of associated factors that unfortunately often contribute to modest therapeutic outcomes or even lack of therapeutic response. Thus, equally, the low adherence especially to topical therapy, the small range of therapeutic agents with optimal safety profile in children, the need to educate the patient and family on psoriasis as a chronic, recurrent disease, avoidance of aggravating factors, psychological impact of the disease on patient and relatives, are key elements that require a special approach in order to increase the effectiveness of therapy [19].

Currently, there are no international treatment standards strictly for pediatric psoriasis, with specialized forums providing adult psoriasis treatment guides that outline a series of therapeutic guidelines for issues targeting the young population affected by the disease. Case studies, case series, reviews, scientific reports are an important and documented source in establishing the right treatment strategy for each case of pediatric psoriasis. The choice of the optimal therapeutic option should consider the patient's age, the severity of the disease, the affected anatomical regions, the impact on quality of life, the presence of comorbidities, the patient's medical history, previous treatments.

Topical treatment

Most cases of pediatric psoriasis can be managed with topical treatment, which is considered first-line therapy. However, most of the products intended for topical application in psoriasis are not intended for pediatric use, which requires their prescription outside the product specifications, in doses adapted to the age of the patients. The range of topical pharmaceutical forms is diverse - creams, ointments, lotions, gels, foams. The choice of the appropriate form for each case should take into account the location of the lesions, the severity of the disease and, last but not least, the patient's preference. Increasing adherence to treatment is one of the goals of pediatric psoriasis management [20].

Topical dermocorticoids are the class of substances most commonly prescribed for the treatment of psoriasis in all age groups. Corticosteroids are available in various concentrations and incorporated into specific vehicles for various localizations and clinical forms. Psoriatic lesions located on the face are treated with mild corticosteroids, while lesions on the body, especially those on the elbows, knees or scalp with moderate or potent dermocorticoids. Studies have shown therapeutic efficacy and safety in the use of topical dermocorticoids in children. Based on this research, it was concluded that halobetasol cream 0.05% and clobetasol propionate 0.05% are some of the most effective and safe substances for the treatment of pediatric psoriasis. The side effects of topical corticosteroid therapy are minimal, the most common being irritation at the site of application, but their use in short courses of treatment is essential to limit the occurrence of side effects [21, 22].

Vitamin D derivatives alone or in combination with dermocorticoids are an alternative to the topical therapy for pediatric psoriasis. Studies have shown the effectiveness of calcitriol and calcipotriol in this category of patients, with minimal side effects such as pruritus or erythema at the site of application. These events are intended to be prevented by avoiding the use of these substances on areas with thin, sensitive skin such as the face, genitals and flexors. Paradoxically, however, it was found that the calcitriol ointment is less irritating than the calcipotriol ointment in intertriginous psoriasis

lesions. The use of vitamin D analogues is not permitted in children under 2 years of age.

Although vitamin D analogues can be used alone, they are often prescribed in combination with topical corticosteroids, a synergistic drug combination that offers the advantage of using a small amount of dermocorticoid and increases adherence to treatment by avoiding separate applications. The combination of calcipotriol-betamethasone propionate has a proven efficacy and optimal safety profile in the treatment of moderate to severe forms of pediatric psoriasis [22].

Other topical agents for the treatment of pediatric psoriasis are calcineurin inhibitors, tacrolimus 0.1% ointment and pimecrolimus 1% cream. Studies have shown that the use of tacrolimus 0.1% twice daily for 30 days in the treatment of psoriasis of the face and flexor regions in children brings net therapeutic benefits, with minimal, reversible local side effects, such as pruritus in only 1% of patients. Regarding the use of pimecrolimus 1% cream in children, there are still no randomized studies on the safety profile. A number of case reports indicate an increased risk of developing lymphomas if pimecrolimus therapy is combined with phototherapy or excessive sun exposure [24].

Phototherapy

An appropriate and highly efficient treatment for pediatric psoriasis is phototherapy. This therapeutic option is addressed especially to clinical forms spread over more than 15-20% of the body surface, to palmoplantar lesions, and to guttate or pustular psoriasis. Phototherapy is also an alternative for children with psoriasis who cannot benefit from systemic treatment. There are three variants of phototherapy: broadband ultraviolet B (BB-UVB, 280-320 nm), narrowband ultraviolet B (NB – UVB, 311-313 nm) and UVA therapy (320-400 nm). The mechanism of action consists in inhibiting DNA synthesis, keratinocyte proliferation by inducing T lymphocyte apoptosis and stimulating the synthesis of anti-inflammatory mediators [25, 26].

The NB-UVB variant is currently considered first-line phototherapy, given the minimal side effects compared to the other two available variants. A number of short-term reactions such as cutaneous xerosis, pruritus and erythema have been reported in the pediatric population, but the long-term side effects of NB-UVB phototherapy such as premature aging or carcinogenesis have not been reported in children receiving this treatment. Concomitant use of topical therapy with acitetrin or calcipotriol is not recommended given the carcinogenic potential of this combination. NB-UVB phototherapy is considered the most effective and safe method of phototherapy for pediatric psoriasis, including forms of guttate or pustular psoriasis.

A disadvantage of this method of treatment is that it is not suitable for infants and young children, for who an unsupervised session in the phototherapy room is impossible.

PUVA phototherapy is rarely used in children due to long-term harmful effects and is contraindicated in children aged less than 12 years due to liver toxicity, digestive and ocular side effects, strong photosensitization [27, 28].

Systemic therapy. Conventional systemic medication

Severe or refractory plaque psoriasis (psoriasis vulgaris), pustular psoriasis, erythrodermic psoriasis and psoriatic arthritis require systemic therapy. Conventional systemic medication for pediatric psoriasis contains the same active substances as in adults: acitretin, retinoids, immunosuppressants-methotrexate and cyclosporine. None of these drugs are approved by the FDA for the treatment of psoriasis in children due to the lack of randomized trials for this age group. Data on the benefits and risks of these therapies generally come from studies based on their long-term use in other pathologies such as ichthyosis (acitretin), juvenile rheumatoid arthritis (methotrexate) or organ transplantation (cyclosporine). Given these aspects, systemic treatment in children with psoriasis is strictly reserved for cases refractory to topical therapy or phototherapy. Low-dose systemic medication may be combined with topical therapy/phototherapy to increase efficacy and reduce the risk of adverse effects [29, 30].

According to a recent study in France conducted on a group of 154 children with moderate-severe psoriasis, acitretin, methotrexate and cyclosporine are first-line systemic therapeutic agents in pediatric psoriasis with optimal safety profile. Acitretin has been shown to be effective for pustular and palmoplantar clinical forms, methotrexate for plaque and guttate psoriasis, and cyclosporine has induced favourable therapeutic effects in cases of erythroderma and palmoplantar psoriasis.

The choice of the systemic therapeutic agent appropriate to age and clinical form is a challenge in the absence of standardized therapeutic protocols. Under these conditions, the approach preferred by clinicians is to treat active surges with doses with an optimal safety profile and, subsequently, to control the disease in the long term by using the lowest possible doses to prevent the occurrence of adverse effects [31].

Biological therapy

Biologics are a new class of pharmacological agents directed against the proinflammatory pathogenic targets of psoriasis vulgaris. In the last decade, numerous randomized studies have confirmed the efficacy of biologic therapy with tumour necrosis factor inhibitors (TNFα-etanercept, infliximab, adalimumab) or with 12/13 interleukin antagonists (ustekinumab). Biological treatment addresses cases of severe psoriasis not responsive to classical topical and systemic medication. Studies on the effectiveness of biological products in children are still limited.

Biological therapy is an attractive therapeutic option for pediatric psoriasis because it offers a convenient administration regimen and rarer clinical-biological reassessments compared to classical therapy. In the future, extensive research on the efficacy, dosage, and safety of long-term administration is needed for the widespread use of these drugs in children [32].

Most studies recommend the use of Etanercept as a biological agent for psoriasis in children and adolescents. The molecule inhibits TNFα activity, the rate of administration is twice a week by subcutaneous injection. The European Commission approved in 2009 etanercept for the treatment of plaque psoriasis, a severe form, refractory to classical systemic therapy, in children over 6 years of age.

The safety and efficacy of etanercept therapy in children with psoriasis were demonstrated through a randomized, double-blind, phase III clinical trial that included 211 patients, children and adolescents aged 4 to 16 years, diagnosed with moderately-severe plaque psoriasis. Patients were treated with etanercept 0.8 mg/kg/week for 12 weeks, with a maximum dose of 50 mg. No opportunistic infections (including tuberculosis), demyelinating diseases, tumours or deaths were identified in this study group. The only mild and transient side effects were pain at the injection site, pharyngitis, bronchitis, or digestive disorders [33, 34].

In 2008, the FDA approved adalimumab therapy for juvenile rheumatoid arthritis in children over 2 years of age. Recently, adalimumab received European Union's approval for administration in cases of severe pediatric psoriasis, unresponsive to phototherapy and conventional systemic medication. There have been published only a few official reports describing the treatment of juvenile psoriasis, Chron's disease and ulcerative colitis with adalimumab given at a dose of 40 mg every 2 weeks. The therapeutic results were favourable, with no noticeable side effects.

Infliximab is not recommended in pediatric psoriasis due to the high rate of malignancy associated with its administration in children [35].

Ustekinumab is a fully human monoclonal antibody that inhibits the p40 protein subunit shared by IL-12 and IL-23, approved by the FDA for the treatment of moderate to severe psoriasis in children over 12 years of age. The dose is adjusted according to weight, and the possibility of easy administration of the product every 12 weeks is an attractive option for the pediatric population. Data on the use of ustinumab for the treatment of children with psoriasis are limited. There are only three reported cases of pediatric patients with severe plaque psoriasis successfully treated with ustekinumab. The efficacy and safety of this treatment were recently evaluated in a randomized, double-blind study involving 110 adolescents (aged 12 to 17 years). 80.6% of the adolescents who received the standard dose of

0.750 mg/kg) reached PASI = 75 after 12 weeks of treatment [36].

Certolizumab is an FDA-approved TNF-α inhibitor for the treatment of psoriasis and psoriatic arthritis in adults, but is not currently approved for pediatric use. Biological therapy with Certolizumab effectively treats patients with idiopathic juvenile arthritis with a similar safety profile to other TNF-α inhibitors. Certolizumab plasma concentrations in children and adolescents are largely within the range observed in adults. Clinical trials are currently investigating the efficacy and safety of this molecule in pediatric arthritis and Crohn's disease, but not in pediatric psoriasis.

Secukinumab and Apremilast are two biologics approved by the European Medicines Agency for the treatment of psoriasis in adults. Secukinumab is a human monoclonal antibody that inhibits interleukin 17A, and Apremilast acts by inhibiting phosphodiesterase 4. There are no case reports or any other specialized studies regarding the use of these new drugs in children and adolescents with psoriasis.

Other biological substances such as ixekizumab, guselkumab, brodalumab, currently approved for the treatment of psoriasis in adults are still undergoing clinical trials for use in pediatric psoriasis. Risankizumab is studied in adolescents with atopic dermatitis [37].

Conclusions

Psoriasis vulgaris is a chronic inflammatory with onset in childhood in about one-third of the cases, and the trend in prevalence and incidence is constantly increasing. Therefore, clinicians should consider psoriasis as a suspected diagnosis at all ages. Particular clinical manifestations and fluctuating evolution make it more difficult to diagnose the disease in children compared to adults.

The therapeutic strategy of pediatric psoriasis should be guided by the risk-benefit ratio taking into account the particularities of age. Also, increasing adherence to treatment remains a desideratum of psoriasis therapy in children. This goal can be achieved by choosing drugs with easy administration and rapid therapeutic effects, but also by regular and sustained doctor-patient-tutor communication.

The affecting of the quality of life especially from the perspective of social integration of the child/adolescent with psoriasis requires the introduction of psychological supportive methods in the management strategy of juvenile psoriasis.

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Conflict of interest
NONE DECLARED

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