Hidradenitis suppurativa in pediatric patients

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Interest in and research on hidradenitis suppurativa (HS) have increased during the past decade, resulting in expanded knowledge about associated comorbidities and treatment efficacy. Knowledge about pediatric-onset HS is still limited, based on case studies, small case series, and extrapolation from adult studies. With increasing prevalence of childhood obesity, decreasing pubertal age, and increasing awareness of HS, physicians may start encountering younger HS patients. This review presents an updated discussion on the epidemiology, pathophysiology, and associated comorbidities in HS, with a focus on pediatric and adolescent patients. It also suggests recommendations for investigation and treatment based on current evidence. (J Am Acad Dermatol 2022;86:140-7.)

Hidradenitis suppurativa (HS) is a chronic skin condition of the hair follicles, characterized by recurrent deep-seated, painful, inflammatory lesions in intertriginous areas such as the axillae, inguinal and anogenital regions.[1] Since the last review on pediatric HS in 2015,[2] there has been an expansion of knowledge about it, although largely based on adult studies. In this article, we discuss an updated review of the epidemiology, presentation, associated comorbidities, and treatment of HS, with a focus on the pediatric age group.

EPIDEMIOLOGY

HS lesions typically start to develop in adolescents and young adults, with an average age of onset of 20 years.[3-5] A bimodal distribution with a smaller later onset peak in the mid-40s has also been reported.[3]

The reported highest prevalence rates by age groups vary significantly between studies, varying between 20 to 60 years of age.[4,6-8] In the United States, the overall estimated point prevalence of HS is 98 per 100,000 persons, and this is maximal at 170 per 100,000 persons in those aged 30 to 39 years.[6] The point prevalence of HS among individuals aged 15 to 17 and 10 to 14 years was 114 and 27 per 100,000 persons, respectively. This further decreased to 2 per 100,000 years in patients younger than 9 years,[9] supporting a disease onset in later adolescence.

CLINICAL CHARACTERISTICS OF PATIENTS WITH EARLY-ONSET HS

A study from the Netherlands of 855 HS patients reported early onset of symptoms before aged 13 years in 66 individuals (7.7%).[10] Two studies found a higher proportion of female patients in the early-onset group compared with the later-onset group,[10,11] whereas a separate study reported patients with prepubescent onset as more likely to be male individuals.[12] The association between sex and age of onset of symptoms thus remains to be clearly established. Although HS is more prevalent in female individuals in Western populations, data from Asian countries have shown the reverse, with an overall increased proportion of male patients.[5,13-18]

The prevalence of HS in patients with Down syndrome is increased,[19-22] with an earlier mean age of onset of 14 years compared with 23 years in HS patients without Down syndrome.[19,20] Additional studies are required to elucidate the pathomechanism for this association.

In 4 studies comparing early onset of HS (defined as reported age of onset younger than 13, 16, 17, and 21 years) and later onset, patients with early-onset HS were approximately twice as likely to report a positive family history.[10,11,23,24]

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One study found an increased number of affected sites in patients with earlier onset,[10] whereas the other 2 found no difference.[23,24] All 3 studies examining disease severity found no difference in patients with an earlier onset, even after adjusting for age of the patient at study enrollment.[10,23,24] This may suggest that patients with a genetic predisposition to HS are not at higher likelihood of more severe disease[25] despite an earlier onset.

CAPSULE SUMMARY

- Investigations for comorbidities such as metabolic syndrome or androgen excess should be performed on an individualized basis for patients with suspected features.
- Physicians should take into account objective disease severity, the effect on the child's emotional, mental, and developmental health, and medication adverse effects in personalizing a treatment plan.

PATHOGENESIS

The pathogenesis specific to a pediatric HS population has not been studied, to our knowledge, and data are extrapolated from basic science and clinical studies in adults.

The development of HS results from an interplay of genetic and environmental factors.[26] The initiating event is thought to be follicular hyperkeratosis and occlusion, followed by rupture of the dilated pilosebaceous unit. This releases follicular contents such as sebum and keratin into the surrounding dermis, inducing a strong chemotactic response from lymphocytes, macrophages, and neutrophils, which subsequently leads to abscess formation.[26] Bacterial colonization, dysbiosis, and formation of biofilms are considered secondary phenomena that further sustain the cycle of chronic inflammation.

The genetic basis of HS continues to be elucidated. A study by Pink et al[27] suggested that monogenic mutations (such as in *NCSTN, PSEN1,* and *PSENEN* genes, which encode γ-secretase enzyme) are responsible for only a minority of HS cases (<7%). This suggests influence of other factors, including polygenetic aberrations and environmental influences. HS patients have also been found to have elevated levels of cytokines, including tumor necrosis factor and interleukin 17, 12, 23, and 36a.[28] A more extensive discussion of the pathogenesis is presented in a separate review.[28]

COMORBIDITIES AND ASSOCIATIONS

Case control studies show higher rates of acne, obesity, inflammatory bowel disease (IBD), inflammatory joint disease, Down syndrome, anxiety and depression in pediatric HS patients compared to controls.[29-31] The prevalence of comorbidities in pediatric aged HS patients[11,29-33] (Table 1) are similar to adult studies showing increased prevalence of metabolic comorbidities, IBD and psychiatric comorbidities among adult HS patients.[34-36]

A few additional studies reported prevalence of comorbidities for patients with a pediatric age of symptom onset (Table I). These have shown relatively high rates of metabolic comorbidities, although most of these patients were adults at data collection.[5,10,23,24]

The association of early-onset HS with hormonal imbalance and premature adrenarche is unclear. From a pathogenesis perspective, the association of HS with androgen-dependent sebum production, apocrine gland maturation, and terminal hair development may explain why HS is rare in prepubertal patients. Obesity and hyperinsulinemia increase androgen levels through direct stimulant effect on ovarian androgen secretion and reduction of serum sex-hormone-binding globulin, increasing free testosterone.[37,38] It is perhaps logical to expect that patients with early-onset HS have a higher degree of dysregulated hormonal balance.

There have been case reports of HS patients younger than 10 years with precocious puberty, [39-41] and a multicenter series of 140 pediatric HS patients found 5 (3.6%) with precocious puberty.[32] However, the study by Tiri et al[29] of 153 pediatric HS patients did not find any with premature adrenarche or adrenal hyperplasia, although this may be limited by the usage of diagnostic codes and lack of active testing. Prepubertal HS patients with normal androgen profiles have been described in case reports,[42,43] and small case series in adults have generally not shown any significant elevation in plasma androgen levels,[44-46] although further well-conducted studies are required to confirm this finding. Clinical evidence to support the effect of hyperandrogenism in HS pathogenesis is at present inconclusive. Androgen hypersensitivity, if present, may instead be relevant in most patients at a more local level of the pilosebaceous unit.[47]

The presence of psychiatric comorbidities depends on the population studied and identification method. In a study from Finland, comorbidities of anxiety and depression were the most common diagnostic codes, affecting 15.7% of HS patients at aged 18 years and increasing to 23.5% by aged 23 years.[29] This outweighed the prevalence of other

Abbreviations used:

HS: hidradenitis suppurativa
HbA1c: glycated hemoglobin

comorbidities such as obesity, hypertension, diabetes, and autoimmune diseases. In a separate study from Israel, however, none of the 248 HS patients and 494 controls younger than 20 years had a diagnostic code of either anxiety or depression.[48]

INVESTIGATIONS

HS is a clinical diagnosis. Investigations, if required, are directed at screening for associated comorbidities and in the formulation of a treatment plan.

There are no guidelines on the types of investigations required in adults or children with HS. Because of the paucity of studies in pediatric HS, and specifically the lack of cost-benefit analysis concerning comorbidity screening, the quality of evidence for any recommendation is low.

As a general approach in line with the North American clinical management guidelines[49] and other authors' work,[2] we recommend targeted investigations that are dictated by the individual's risk for metabolic, autoimmune, and hyperandrogenic comorbidities (Fig 1). These include a detailed history and physical examination looking for features of inflammatory bowel disease, inflammatory arthropathy, precocious puberty, and virilization. A family history of HS and associated comorbidities should be elicited. Measurement of body mass index and blood pressure is easily performed and can be routine. Guided by the history and physical examination, further investigations such as a fasting blood glucose level, glycated hemoglobin level, lipid panel, thyroid testing, hormonal evaluation, and pelvic ultrasonography may be pursued. For patients at high risk of metabolic comorbidities, routine screening for the development of them should be considered even if the initial screening result was negative.

TREATMENT

The management of pediatric HS patients, especially those with more severe disease, is challenging because of the lack of efficacy and safety data of systemic treatments in this age group. Treatment modalities are largely extrapolated from adult populations. A comprehensive review of treatment options in adult HS patients can be found in a separate article.[50] We discuss considerations specific and pertinent to HS patients in the pediatric age group.

Aggressive disease control versus toxicity of treatment

Although it is prudent to select treatment modalities with the fewest adverse effects in young patients because of concerns regarding their development and toxicity of treatment, it is important to be cognizant of the scarring and fibrosis that often result from inflammatory lesions of HS. For a growing child or adolescent, the inflammatory lesions, drainage, pain, and resultant scarring may interfere with activities of daily living such as sports, recreational activities, and schooling. Inability to participate, as well as the negative aesthetic outcome, could severely affect the quality of life of young HS patients. Topical treatments such as clindamycin, resorcinol, and antiseptics are safe but often ineffective in moderate to advanced stages,[50-52] and a treatment regimen that strikes a balance between the avoidance of unnecessary toxicity and the need for adequate disease control is even more pertinent in pediatric HS patients.

Caveats about systemic medication

Systemic antibiotics from the tetracycline class (eg, tetracycline, doxycycline, minocycline) are commonly used in adult HS patients because of their efficacy and relative safety. In children younger than 8 years, the risk of discoloration of permanent teeth and dental enamel hypoplasia has traditionally precluded its use as a class. Doxycycline has a reduced ability to chelate calcium and is hence less likely to result in permanent tooth discoloration. No significant difference in tooth shade or enamel hypoplasia was appreciated in 3 studies of children receiving doxycycline for various indications.[53-55] Therefore, within the tetracycline class, doxycycline is the preferred antibiotic choice for pediatric HS patients. Other antibiotics such as the combination of clindamycin and rifampicin, ertapenem, erythromycin, and metronidazole are suitable for children.[2,56,57] Rifampicin, however, should be used with caution in areas endemic for tuberculosis because of the risk of drug resistance.

Small case series showed oral finasteride at doses of 1 to 10 mg a day to be effective in pediatric HS patients as young as 6 years, with or without precocious puberty.[41,58] Although finasteride is well tolerated, its long-term safety is unknown; in particular, the effect on prostate size, sexual dysfunction, and pubertal development.

The efficacy of systemic retinoids is related to their anti-inflammatory properties and effects on

Table I. Comorbidities in pediatric-HS patients and pediatric-onset HS patients

Comorbidity	Prevalence in pediatric HS patients*	Prevalence in pediatric-onset HS patients†
Overweight, %	18-32[11,30]	30.6-57.5[5,10,11,23]
Obesity, %	5.9-68.7[11,29-31]	21-32.3[5,10]
Diabetes mellitus, %	2.6[29]	2.9-25[5,24]
Hypertension, %	2[29]	5.8-6.3[5,24]
Dyslipidemia, %	—	7.3-62.5[5,24]
Metabolic syndrome, %	2[29]	—
Smoking, %	9-35[11,30,32,33]	11-56.1[5,10,11,24]
Inflammatory bowel disease, %	3.3[29]	1.4-1.5[10,24]
Inflammatory joint disease, %	5.2[29]	—
Down syndrome, %	4.6-5[29,32,33]	—
Thyroid disorders, %	2.6[29‡]	—
Precocious puberty, %	0-3.6[29,32]	0[12]
Polycystic ovarian syndrome, %	0-3.8 of females[29,32]	17.5 of females[12]
Pilonidal sinus/pilonidal cyst, %	1.3-16.4[29,32,33]	40.6%[24]
Scalp dissecting cellulitis, %	—	8.7%[24]
Acne vulgaris/acne conglobata, %	13.7-68%[29,32,33]	23.2%[24]
Depression, %	0-8.5[29,48]	—
Anxiety, %	0-5.9[29,32,48]	—

—, Data not reported; *HS*, hidradenitis suppurativa.
*Cut offs for the definition of pediatric were 16,[11] 17,[30,31] 18,[29,32,33] and 20 years of age.[48]
†Cut offs for pediatric onset in the 6 studies were 13,[10] 16,[5,11] 17,[23] 18,[12] and 21,[24] years of age. Many of these patients were adults at point of data collection.
‡Thyroid disorders were more common in HS patients, this was partially because patients with Down syndrome who also had HS were more likely to have thyroid disease.

follicular hyperkeratinization.[59] Acitretin is best avoided in female patients approaching childbearing potential because of its long-lasting teratogenic effects (3 years from point of drug cessation). Isotretinoin may be used, although caution should be exercised for patients younger than 12 years because of case reports of premature epiphyseal closure.[60,61] The potential teratogenicity of oral medications such as tetracyclines, retinoids, and finasteride should be emphasized to all female patients of childbearing potential.

Adalimumab is presently the first and only Food and Drug Administration–approved biologic for HS. Its approval was expanded in 2018 to include pediatric patients older than 12 years and weighing at least 30 kg, despite the lack of safety data specific to this population.[62] The relatively good safety data extrapolated from other pediatric indications such as psoriasis,[63,64] juvenile idiopathic arthritis,[65] and Crohn's disease[65,66] make it a valuable option for pediatric patients with moderate to severe HS. It is Food and Drug Administration pregnancy category B, and thus its consideration in adolescents is of avail.

Surgery

HS lesions tend to recur after cessation of systemic therapy.[52,67] Given the negative cosmetic consequence, the desire for a cure is especially attractive to younger patients. Several surgical techniques have been described for the management of HS, which range from the minimally invasive "deroofing" techniques to extensive radical excisions that clear all HS lesions in diseased areas, thus potentially leading to long-term cure. A study of 11 patients aged 13 to 17 years who underwent wide local excision and reconstruction found that 57% achieved long-term remission at a mean of 31 months of follow-up. However, postoperative complications, including wound dehiscence, surgical site infection, and scar contracture, were observed in 87%, although most were considered minor.[68]

Addressing psychological comorbidity

Childhood and adolescence pose psychological challenges distinct from those of adulthood, including those related to sexuality and development of self-identity.[69-72] Not uncommonly, we encounter absenteeism from school, bullying, self-isolation, low mood, anxiety, and negative thinking

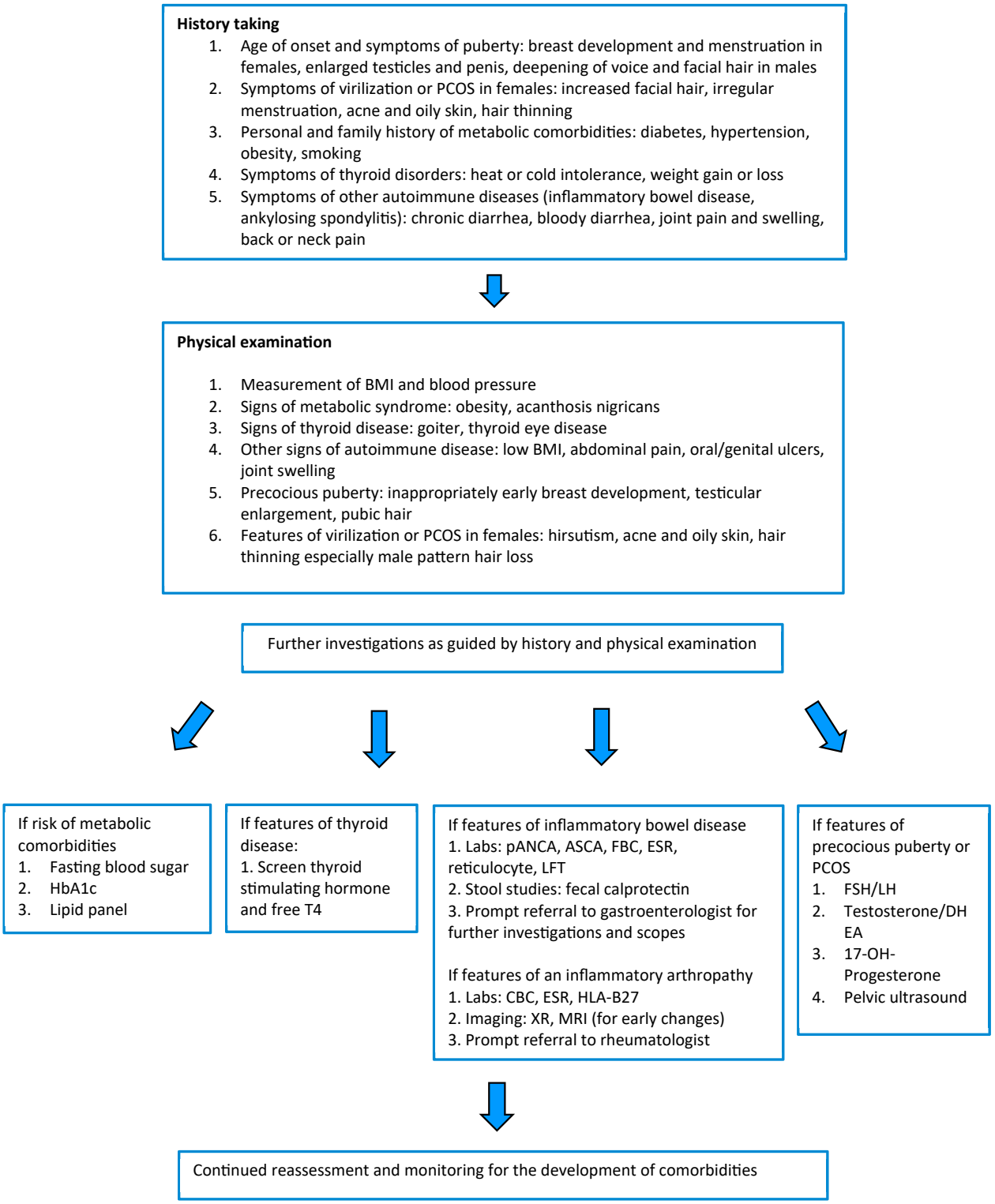

Fig 1. Approach for the workup of comorbidities in pediatric hidradenitis suppurativa patients. *ASCA*, anti saccharomyces cerevisiae antibodies; *CBC*, complete blood count; *DHEA*, dehydroepiandrosterone; *ESR*, erythrocyte sedimentation rate; *FSH*, follicle stimulating hormone; *HbA1c*, glycated hemoglobin; *LFT*, liver function test; *LH*, luteinizing hormone; *MRI*, magnetic resonance imaging; *pANCA*, perinuclear antineutrophil cytoplasmic antibodies; *XR*, radiograph.

in HS patients. Recommendations to consider include active treatment of disease, preemptive pain control, and innovative functional solutions[73,74] to manage discharging lesions. Counseling, healthy role modeling, and patient support groups may help to encourage acceptance, cognitive reappraisal,[75] and development of a healthy disease-related self-identity. Referral to professional psychological and psychiatric support when indicated should be timely.

Of utmost importance in the management of pediatric patients is the effect of HS on parents and the role of parental reinforcement (both positive and negative) on the child's coping. However, as pediatric HS patients transition from childhood to adolescence, physicians would need to progressively balance parental involvement with increasing clinical time alone with the patient because disclosure of sensitive information and autonomy in decision making become more relevant. Finally, HS is a chronic disease that will likely remain with the individual, and expectations for disease control or cure must be managed early in the therapeutic relationship. A better understanding and acceptance of the disease course on the parents' or patients' part lays the foundation for long-term trust between patient and physician.

CONCLUSION

Because of the low prevalence of HS in the pediatric age group, knowledge about pediatric-onset HS is still limited and trailing behind information about HS in adult studies. Similarities with adult patients include the higher prevalence of metabolic comorbidities, inflammatory bowel disease, and psychiatric disorders. The biochemical and genetic profile of pediatric HS patients, significance of an early onset in relation to disease prognosis, and optimal treatment modalities are areas in which knowledge is still significantly lacking, and will be promising fields for future avenues of research.

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