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Research Article

Diagnosis of HyperIgE Syndromes (HIES) on Black Phenotype Patients with Atopic Dermatitis Followed in Dakar, Senegal

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Abstract

This study aimed to determine the epidemiological and clinical-biological manifestation of hyper IgE syndromes during atopic dermatitis in the pediatric dermatology department of the Centre Hospitalier National d'Enfants Albert Royer (CHNEAR) on black phenotype children in Dakar, Senegal. It was a descriptive cohort study including patients with atopic dermatitis who consulted in Hôpital d'Enfants Albert Royer from 1st Janvier 2020 to 31st August 2022. We considered hyper IgE syndrome as any patient with atopic dermatitis, recurrent infections, elevated serum IgE and a National Institute of Health (NIH) score for the diagnosis of hyper IgE syndromes greater than or equal to 20. We collected 27 cases accounting for a frequency of 0.78% among 3438 cases of atopic dermatitis. The mean age was 7 years with a sex ratio of 02. Consanguinity was found in 33.3% of patients. Cutaneous infections were found in 81.5% of cases. Bacterial infections were found in 66.6%. Viral and fungal infections stood for 11.1% and 29.6% respectively. Extracutaneous manifestations were infectious in 29.6% and non-infectious, consisting of facial dysmorphia (85.2%), scoliosis (n=01), joint hyper-extensibility (n=01) and retention of primary teeth (n=01). The mean total IgE level was 6094.7 KIU/L. Hypereosinophilia was found in 63%. The NHIES score was between 20 and 40 in 96.3% and above 40 in 3.7%. The frequency of hyper IgE syndromes in atopic dermatitis is 0.78%. Bacterial infections predominate. A genetic testing is necessary to better describe these HIES.

Keywords: Hyper IgE Syndrome; Atopic Dermatitis; Primary Immuno-Deficiency; NIHES; Pediatric Dermatology; Dakar

Introduction

In our resource-constrained countries, the diagnosis of primary immune deficiency is very challenging for practitioners. Indeed, we face hindrances to suitable immunological and genetic investigations in suspicious situations. However, according to the severity of PID, it is important to suspect them given the unusual clinical patterns and allergic and/or infectious features, particularly severe, in order to improve both the life expectancy and quality of life of the patients. As dermatological manifestations are most often present at all stages of these PIDs (at the beginning, in the middle and at the end), we focused on the hyper IgE syndrome during atopic dermatitis [1]. Hyper IgE syndrome is a combined immunodeficiency syndrome defined by the triple symptom complex of atopic dermatitis, elevated serum IgE and recurrent infections. The clinical-biological similarities between atopic dermatitis and hyper-IgE syndrome mean that patients with hyper-IgE syndrome can be misdiagnosed. However, the National Institute of Health score for the diagnosis of hyper IgE syndromes (NIHES) can help set the diagnosis in our context by including in a follow-up cohort these suspicious patients in the absence of

confirmatory genetic testing and improve life expectancy and quality of life for patients and parents [2]. Amid that atopic dermatitis accounts for more than 50% of our consultations in the pediatric dermatology department of the Centre Hospitalier National d'Enfants Albert Royer (CHNEAR), we conducted this study to determine:

The frequency of hyper IgE syndromes in black phenotype patients followed for atopic dermatitis at the pediatric dermatology department of the CHNEAR. The clinical-biological hallmarks of our patients with hyper IgE syndromes.

Methodology

We conducted a descriptive cohort study over 20 months ranging from 01 January 2021 to 30 September 2022 in the pediatric dermatology department of the CHNEAR. The latter is the reference department for the management of pediatric dermatological pathologies in Senegal. The department carries out a yearly average of 6,000 consultations, with atopic dermatitis accounting for more than 50% of diagnoses. It comprises 3 consultant dermatologists, including a teacher-researcher and doctors specializing in dermatology, as well as paramedics. The study population consisted of all patients with atopic dermatitis seen in the consultation unit of the pediatric dermatology department of CHNEAR. Case definition: any patient of any age with atopic dermatitis, elevated total IgE, more than 3 episodes of skin infection in the year and a NIHES score greater than or equal to 20 was considered to experience hyper IgE syndrome. The NIHES score is attached (Appendix 1).

A questionnaire was used to collect socio-demographic, clinical and paraclinical data. The diagnosis of atopic dermatitis was based on the Hanafin and Rajka criteria. The severity of atopic dermatitis was assessed using the Severity Scoring of Atopic Dermatitis (SCORAD) [3]. The NIHES score was used to assess the likelihood of hyper IgE syndrome in children. The parameters studied for this score included: total IgE levels, eosinophil levels, recurrence of skin infections, recurrence of respiratory infections and osteoarticular, dental and ophthalmological impairments. If the score is > 40 points, hyper IgE syndrome (HIES) is probable; if the score is 20-40 points HIES is possible. Data was entered using Epi info 7 software. Data analysis was performed using SPSS (Statistical Package for Social Sciences) version 18.

Results

Frequency

We collected 27 cases of hyper IgE syndrome based on our case definition with a NIHES score ranging between 20 and 40 in 96,3% of cases (n=26), a score of 42 in 3,7% of cases (n=1). Meanwhile the study period, 6000 patients were seen at the consultation unit of whom 3438 patients underwent atopic dermatitis accounting for 0,78% of patients with atopic dermatitis followed in the pediatric dermatology department of CHNEAR. The 27 cases of hyper IgE syndrome involved 18 boys and 9 girls with a sex ratio of 2. The mean age of patients at the time of diagnosis was 7 years old with extremes of 01year and 25years. The age of our patients was less than 5 years in 33,33% (n=9), between 5 and 9 years in 44,44% (n=12), between 10 and 14 years in 18,52% (n=5), more than 20 years in 3, 71% (n=1).

Clinical-Biological Characteristics

Consanguinity

We found parental consanguinity in 9 patients (33.3%). Consanguinity was 2nd degree in 3.7% (n=01) of cases and 3rd degree in 14.8% (n=04) of cases.

Age of Cutaneous Lesions Onset

The age of cutaneous lesions onset was in the neonatal period in 11.1% (n=3), less than 3 years in 18.5% (n=5), between 3 and 5 years in 33.3% (n=9) and between 5 and 10 years in 14.8% (n=4).

Atopic Manifestations

Besides atopic dermatitis, personal atopic symptoms such as asthma, LCET and allergic rhinitis were found in 29.6% (n=08), 40.7% (n=11) and 40.7% (n=11) of patients respectively. Patients had more than 2 signs of atopic conditions such as asthma, allergic rhinitis and allergic conjunctivitis in addition to atopic dermatitis in 29.6% (n=8). A family history of atopy in the 1st-degree relative was found in 92.6% of cases (n=25). A food allergy detected by allergological tests was found in 37% of cases (n=10). The allergens found were: milk, blackfish, seafood, peanuts and charcuterie.

Non-Infectious Dermatological Manifestations

All patients underwent atopic dermatitis. Thus, acute eczema and chronic eczema accounted for 51,8% (n=14) and 85,1% of cases (n=23) respectively (Fig. 1). The severity of Atopic Dermatitis (AD) was assessed on every patient using the SCORAD. AD was mild in 9% of cases (n=4), moderate in 30,4% of cases (n=7) and severe in 69,6% of cases (n=16) (Fig. 2). Apart from atopic dermatitis, erythroderma was found in 3 patients of whom 1 experienced congenital bullous ichthyosiform erythroderma (Fig. 3).

Infectious Dermatological Manifestations

A mucocutaneous infection was found in 22 patients (81.48%). These infections were bacterial in 66.6% (n=18) (Fig. 4), viral in 11.1% (n=03) (Fig. 5) and fungal in 29.6% (n=08) (Fig. 6).

Infectious Extra-Dermatological Manifestations

Extracutaneous infection was found in 29.6% of cases (n=8). They comprised respiratory infections in 22.2% (n=7), osteitis and lymph node and digestive tuberculosis in 3.7% of cases each (n=1). Respiratory infections included bronchiolitis in 18.5% (n=5), common germ pneumonia in 3.7% (n=1) and pulmonary tuberculosis in 3.7% (n=1). In the case of tuberculosis, the patient presented with multifocal tuberculosis of the skin (miliary type), lungs, lymph nodes and digestive tract.

Non-Infectious Extra-Dermatological Manifestations

Non-infectious extra-dermatological manifestations comprised:

Facial dysmorphia in 85.2% of cases (n=23), characterized by a prominent forehead and flattened nasal root

Cardiac manifestations characterized by mitral and tricuspid regurgitation in 3.7% of cases (n=01)

Osteoarticular manifestations in 11.1% (n=03). They included: joint pain (3.7%, n=01), scoliosis (3.7%n=01), arthritis (3.7%, n=01), joint hyper-extensibility (3.7%, n=01)

Dental abnormalities characterized by retention of primary teeth in 3.7% of cases (n=01)

Digestive disorders characterized by abdominal pain in 7.4% of cases (n=02)

Neuropsychiatric manifestations in 18.5% of cases (n=05). They were characterized by a delay in psychomotor development in 11.1% of cases (n=03), a disorder in social interaction in 3.7% of cases (n=01)

Severe acute malnutrition in 3,7% of cases (n=01).

Biological Characteristics

Total IgE

Total IgE was elevated in all cases and greater than 2000 KIU/L. The mean total IgE level was 6094.7 KIU/L. The value was: greater than 2000 KIU/L in 81.5% of cases (n=22); between 1000 and 2000 KIU/L in 11.1% (n=3); between 300 and 1000 KIU/L in 7.4% (n=2).

Hemogram Disorders

Hypereosinophilia was noted in 63% (n=17), neutropenia and lymphopenia in 7.4% of cases each (n=2) and monocytosis and thrombocytosis in 29.6% of cases each (n=8). Anemia was found in 11.1% of cases (n=3).

Germs Causing Infections

Bacteriological sampling was only possible in 22.2% of cases (n=6). The germs isolated were: *Mycobacterium tuberculosis*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Proteus mirabilis* in 1 case each.

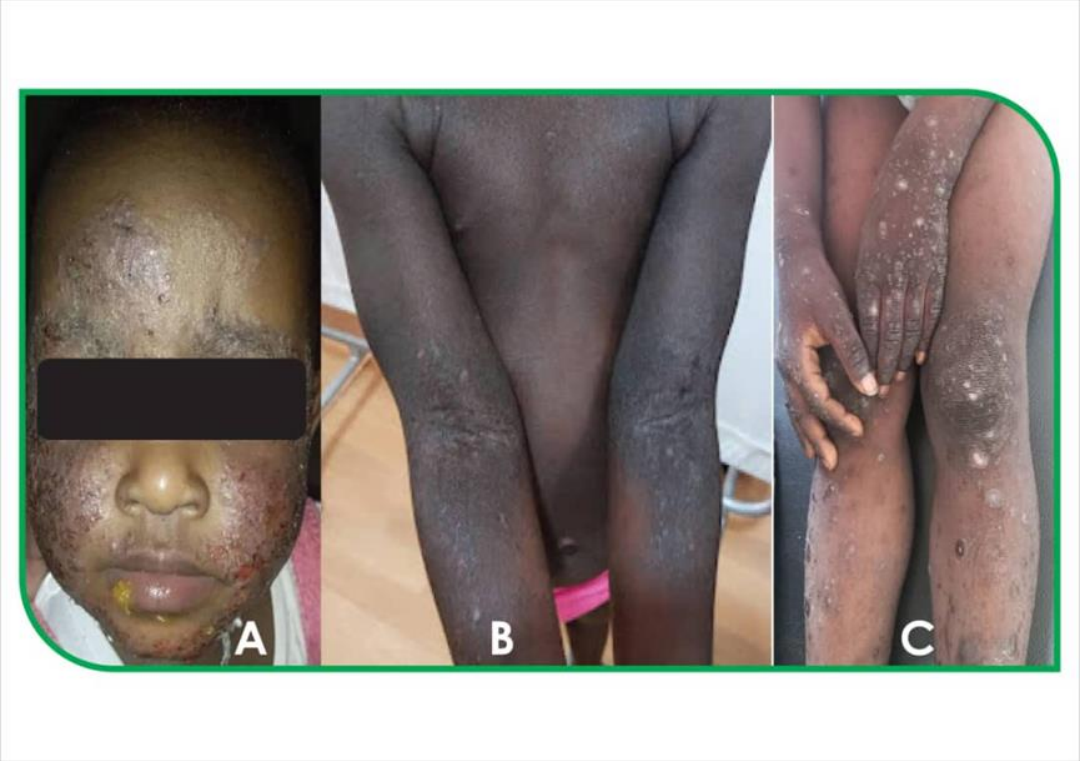

Figure 1: Acute and chronic signs of atopic dermatitis in children with hyper IgE syndrome. A: Acute eczema with diffuse erythematous, vesicular, excoriated and weeping lesions; B: Chronic eczema with diffuse lichenification predominating in the folds; C: Chronic eczema with lichenified lesions associated with annular scars with a desquamative collar indicative of impetigo in the cicatricial phase.

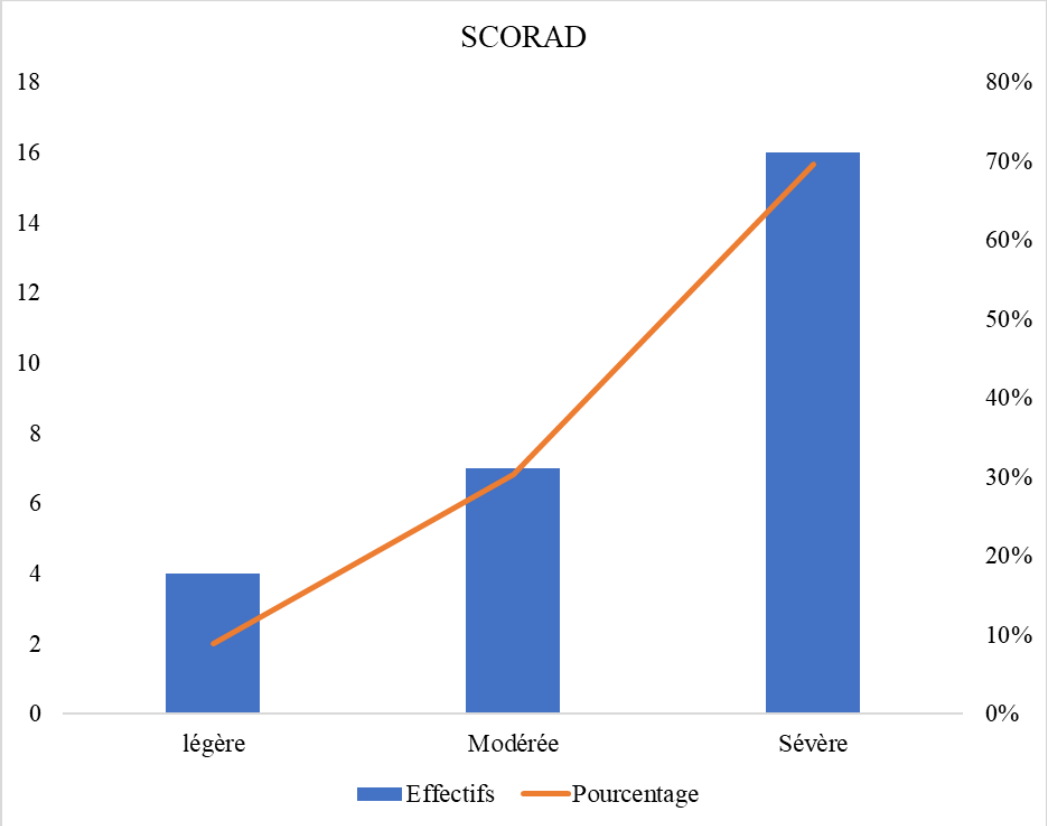

Figure 2: Severity of atopic dermatitis according to Scorad.

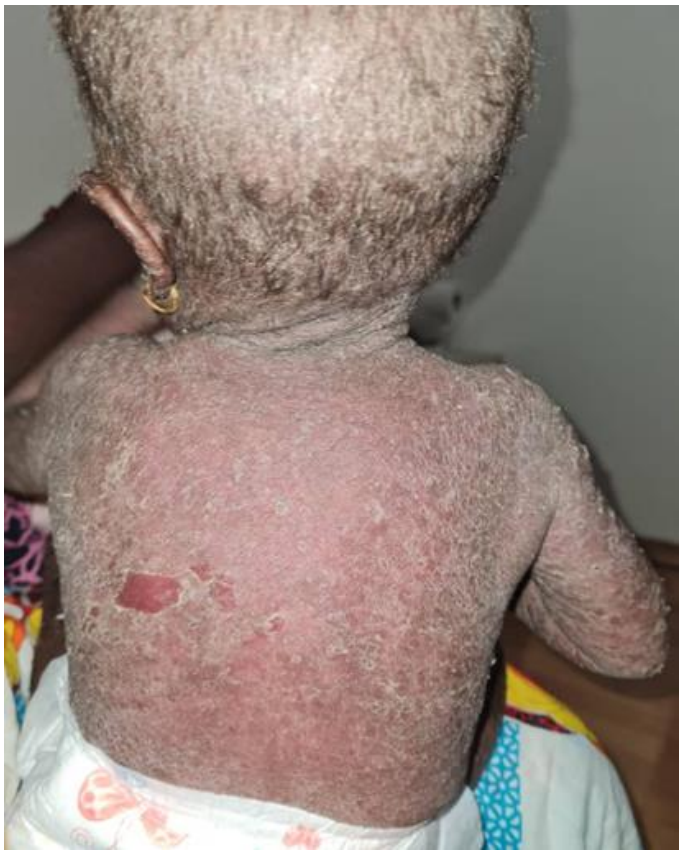

Figure 3: Congenital bullous ichthyosiform erythroderma.

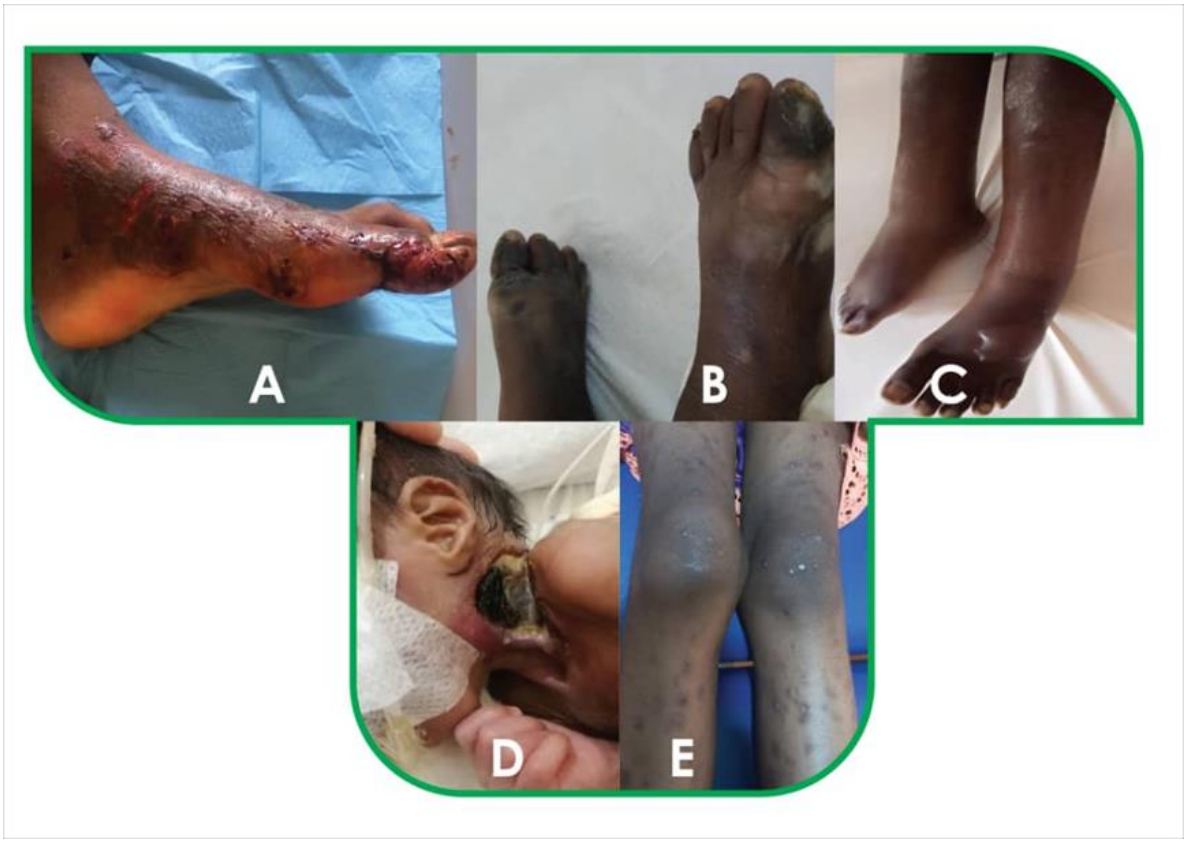

Figure 4: Bacterial dermatoses. (A,B): Severe pyodermitis: 77,77%, n=21; (C): Erysipla: 3,7%, n=1; (D): Ecthyma: 3,7%, n=1; (E): Miliary cutaneous tuberculosis: 3,7%, n=1.

Figure 5: Viral dermatoses. A: Oral papillomatosis in a patient with hyper IgE syndrome; B: Giant anal condyloma; C: Disseminated wart.

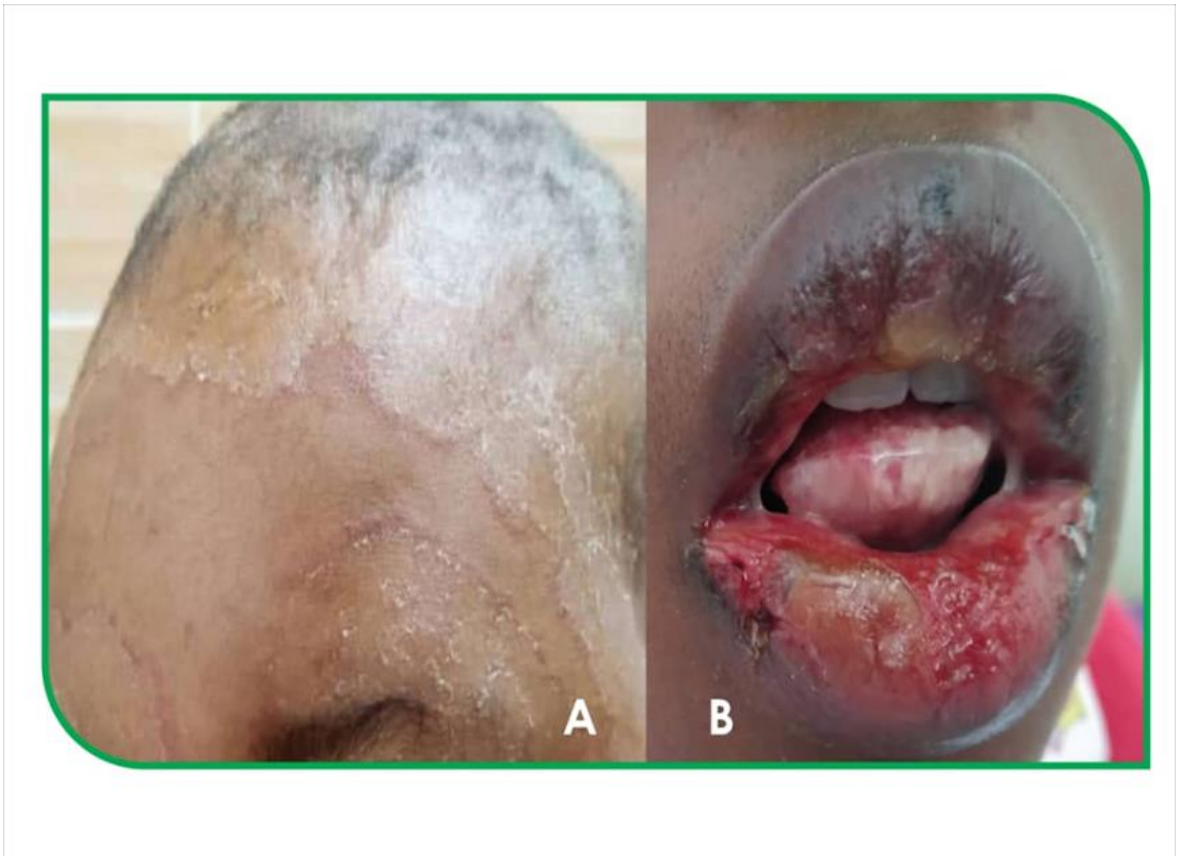

Figure 6: Fungal dermatoses. A: Hairless skin dermatophytosis (14,8%, n=4); B: Oral esophageal candidiasis (n=4).

Discussion

We conducted a descriptive cohort study of patients with atopic dermatitis followed at the pediatric dermatology department of CHNEAR to determine the frequency of HIES in this population, as well as their clinical and biological characteristics. We chose this methodology because of the scarcity of hyper-IgE syndrome. Actually, in Senegal, apart from the 14 cases reported in the article by Ndiaye Diop, et al., in 2022 [1], the literature is scanty. And worldwide, reported cases remain sporadic. This study is the first cohort study of patients with HIES in Senegal and particularly in sub-Saharan Africa, to improve their diagnosis and follow-up.

We reported 27 cases out of 3,438 patients with atopic dermatitis, representing a frequency of 0.78% in patients treated for atopic dermatitis in the pediatric dermatology department of CHNEAR and an annual frequency of 16 patients/year. As hyper IgE syndrome is an uncommon disease and difficult to diagnose, there are few prevalence studies and its annual incidence worldwide is estimated at around 1/1,000,000 [4]. In Morocco, Bousfiha, et al., reported 48 cases in 15 years, representing a frequency of 3 cases yearly [5]. Similarly, in China, in 2017, some authors reported 28 patients with HIES out of 575 patients with DIP registered between June 2008 and July 2016 (8 years). This represents a frequency of 4.97% of DIP in China and an annual frequency of 3.5 cases of hyper IgE syndrome per year (2,4). In the United States, in 2018, some authors reported 85 cases of hyper IgE syndrome recorded between 2001 and 2016 (15 years), based on the USIDNET (United States Immunodeficiency Network) registry created in 1992. The patients came from 25 different American States and Quebec. This represents an annual frequency of 5.7 cases of hyper IgE syndrome per year in the United States [7]. These results are much lower than our findings. This could be linked to a selection bias. In fact, atopic dermatitis, which is one of the elements in the diagnostic triad of hyper IgE syndrome, is one of the main reasons for consultation at the pediatric dermatology department of CHNEAR, accounting for more than 50% of consultations during the study period.

The mean age of our patients at diagnosis was 7 years. A synthetic study including 09 studies carried out between 2012 and 2021 in Europe, Asia and the United States reported that diagnosis was made at a mean age of 10.2 years [8]. Gernez Y, et al., reported a median age of onset of symptoms of 2 years [7]. Thus, the diagnosis is made at a fairly late age compared to the appearance of the first signs. This result reflects a delay in the diagnosis of hyper IgE syndrome that contributes to the seriousness of the disease, due to the lack of specific follow-up and vital prone-threat complications.

The sex ratio was 2 with a male predominance. This trend was also reported in the USA in 2016 by Gernez, et al., [7]. Unlike, Wu J, et al., in China reported more women with a sex ratio of 8/9 [6].

Consanguinity was found in 33.3% of patients. In the literature, familial features have rarely been described [4]. However, in Africa, particularly in the north, cases have been described, especially autosomal recessive forms, associated with consanguinity. The first cases of hyper IgE syndrome caused by a mutation in the PMG3 gene were described in patients from two consanguineous Tunisian families [9].

Manifestations of atopy other than atopic dermatitis were present in 77.7% of patients. A food allergy was found in 37% of patients. A study carried out by Hernandez-Trujillo, et al., in the USA in 2004 reported an allergy to cow's milk in a patient with hyper IgE syndrome [10].

Recurrent skin infections are one of the clinical hallmarks of hyper IgE syndrome. A skin infection was found in 81.48% of patients. Bacterial infections were more frequent, occurring in 66.6% of patients. Unlike, in 2021, Saikia, et al., reported a slightly higher frequency (77.8%) in India [11]. However, in 2019, Lorenzini, et al., (Italy) and Xiang, et al., (China) reported 70% of fungal skin infections, which is more than two-fold the frequency of fungal infections (29.6%) reported in our cohort [10,11]. Viral infections affected 11.1% of patients in our study; these results are slightly similar to those of Chandesris et al who reported few viral skin infections (13%) in a study carried out in 2012 [6,14].

Regarding extracutaneous infectious manifestations, they were found in 29.6% of patients, including multifocal tuberculosis with lungs, lymph nodes and digestive tract involvements. Atopic dermatitis, a core element for the diagnosis of hyper IgE syndrome, was found in all our patients. These results corroborate with those of Wu J, et al., who also reported the presence of AD in 100% of patients in a study carried out in 2017 in Shanghai [6].

Non-infectious extracutaneous manifestations helped to confirm the diagnosis in accordance with the NIHES score. They comprised: facial dysmorphia (85.2%), scoliosis (n=01), joint hyper-extensibility (n=01) and primary teeth retention (n=01). The mean total IgE level was 6094.7 KIU/L. Gernez, et al., reported a mean serum IgE level of 8383.7 KIU/mL [7]. In the same study, primary teeth were retained in 41.4% of cases, fractures in 39% and scoliosis (34.1%). This greater frequency of non-infectious extradermatological manifestations may be explained by the fact that the STAT 3 mutation is the main cause of hyper IgE syndromes in their cohort.

Regarding paraclinical data, hypereosinophilia was found in 63% of cases. In 2018, Gernez, et al., reported a frequency of 70% [7]. Additionally, thrombocytosis (29.6%), lymphocytosis (25.9%) and monocytosis (29.6%) were also found. Total IgE levels were high in all patients, with 81.5% having levels more than 2000 KIU/L. The NIHES score, used for hyper IgE syndrome diagnosis, was assessed in all our patients. In 96.3% of the study population, the diagnosis was possible while it was probable in 3.7% of patients. However, the NIHES score is more sensitive and more specific when the STAT3 mutation is present, with scores > 40. In autosomal recessive forms of hyper IgE syndrome, the NIHES score is less sensitive. Genetics is therefore still a paramount argument for the diagnosis of hyper IgE syndrome.

Conclusion

At the end of this work, we outlined the frequency of hyper IgE syndromes in patients with atopic dermatitis followed at the pediatric dermatology department of CHNEAR, which accounted for 0.78%. The mean age at diagnosis was 7 years, a male predominance. Clinical-biological manifestations were dominated by cutaneous infections, particularly bacterial, respiratory infections, severe atopic dermatitis and elevated total IgE antibodies, with a mean level of 6094.7 KIU/L and a level greater than 2000 Kui/L in 81.5% of cases and eosinophilia in 63% of cases. The NIHES score ranged from 20 to 42. In the prospects, we will determine the genetic mutations responsible for hyper IgE syndrome in our study population.

Conflicts of Interests

The authors declare that there is no conflict of interest for this paper.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

M.T.N.D. wrote the first draft of the article.
M.T.N.D. A.A.B., K.D. put forward the hypothesis of research into hyper-IgE syndromes on dark skin and coordinated the work.
B. S. F.D.F., A.D., B.N., I.D. I.D.B., M.L.F., P.M.F., M.N., M.D., O.N., F. L. were involved in patient care
K.D. collected data on the questionnaire and data collection form
S.Oumou NIANG coordinate the work.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

The content of this article has been examined in accordance with the rules laid down by the "Comité National d'Ethique pour la Recherche en Santé (CNERS)" of Senegal and in accordance with the procedures established by the "Université Cheikh Anta DIOP de Dakar" (UCAD) for the ethical approval of any research project involving human and animal participants. The UCAD Research Ethics Committee (Comité d'Ethique de la Recherche - CER) considers that the appropriate ethical standards have been respected. (Réf.: CER/UCAD/AD/MSN/0001/2024).

Consent to Participate

Written informed consent was obtained from the parents.

Consent to Publish

The authors affirm that human research participants provided informed consent for publication of the images in Fig. 1, 3, 4 and 5.

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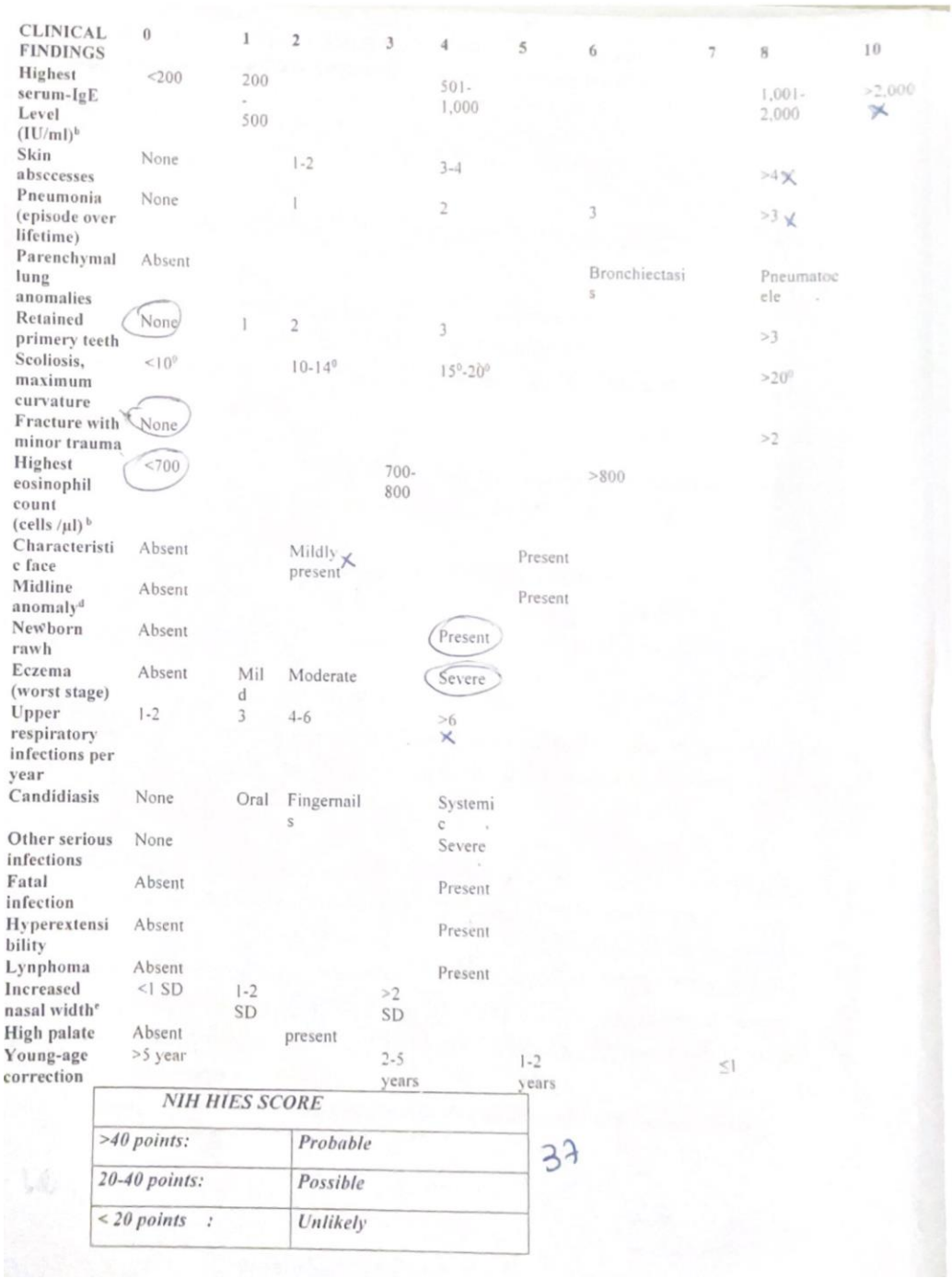

CLINICAL FINDINGS	0	1	2	3	4	5	6	7	8	10
Highest serum-IgE Level (IU/ml)[b]	<200	200 - 500			501-1,000				1,001-2,000	>2,000
Skin absccesses	None		1-2		3-4				>4	
Pneumonia (episode over lifetime)	None		1		2		3		>3	
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele	
Retained primery teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	<10[0]		10-14[0]		15[0]-20[0]				>20[0]	
Fracture with minor trauma	None								>2	
Highest eosinophil count (cells /µl)[b]	<700			700-800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly[d]	Absent					Present				
Newborn rawh	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper respiratory infections per year	1-2	3	4-6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lynphoma	Absent				Present					
Increased nasal width[e]	<1 SD	1-2 SD		>2 SD						
High palate	Absent		present							
Young-age correction	>5 year			2-5 years		1-2 years		≤1		

NIH HIES SCORE	
>40 points:	*Probable*
20-40 points:	*Possible*
< 20 points :	*Unlikely*

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Appendix 1: NIH score of one patient = 37.