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HLH as an additional warning sign of inborn errors of immunity beyond familial-HLH in children: a systematic review

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Background: Hemophagocytic Lymphohistiocytosis (HLH) is a rare and life-threatening condition characterized by a severe impairment of the immune homeostasis. While Familial-HLH (FHL) is a known cause, the involvement of other Inborn Errors of Immunity (IEI) in pediatric-HLH remains understudied.

Objective: This systematic review aimed to assess the clinical features, triggers, laboratory data, treatment, and outcomes of pediatric HLH patients with IEI other than FHL (IEInotFHL), emphasizing the importance of accurate identification and management.

Methods: A systematic search for studies meeting inclusion criteria was conducted in PubMed, EMBASE, MEDLINE, and Cochrane Central. Quality assessment was performed through JBI criteria.

Results: A comprehensive search yielded 108 records meeting inclusion criteria, involving 178 patients. We identified 46 different IEI according to IUIS 2022 Classification. Combined immunodeficiencies, immune dysregulation disorders, and phagocyte defects were the IEI most frequently associated with HLH. In 75% of cases, HLH preceded the IEI diagnosis, often with an unrecognized history of severe infections. Triggers reflected the specific infection susceptibilities within IEI groups. Liver and central nervous system involvement were less common than in FHL cases. Treatment approaches and outcomes varied, with limited long-term follow-up data, limiting the assessment of therapeutic efficacy across IEI groups.

Conclusion: A comprehensive evaluation encompassing immunological, infectious, and genetic aspects is essential in pediatric-HLH. Relying solely on FHL or EBV susceptibility disorders tests is insufficient, as diverse other IEI can contribute to HLH. Early recognition of HLH as a potential warning sign can guide timely diagnostic investigations and facilitate tailored therapeutic interventions for improved outcomes.

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KEYWORDS

hemophagocytic lymphohistiocytosis, inborn errors of immunity, macrophage activation syndrome, immune deficiency, familial hemophagocytic lymphohistiocytosis, hemophagocytic syndrome

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, hyper-acute and potentially life-threatening clinical entity caused by a severe impairment of the immune homeostasis. Previously seen and managed as a single disease, HLH represents a potential clinical expression of several diseases. HLH occurring in patients bearing known mutations in genes related to granule-dependent cytotoxicity are termed "primary" or familial HLH (FHL) (1). According to the International Union of Immunological Societies (IUIS) (2), FHL are Inborn Errors of Immunity (IEI) presenting with HLH as their predominant clinical feature. On the contrary, when HLH is triggered by infections, autoimmune manifestations or malignancy in the absence of specific mutations in FHL-related genes, it is termed "secondary" or "acquired" (1). However, this classification may be considered overly simplistic, since primary HLH are often triggered by infections or other events that activate the immune system as well as secondary HLH might hide unrecognized or unknown genetic causes. Moreover, since HLH both primary and secondary stems from a loss of immune homeostasis, several IEI other than FHL (IEInotFHL) could predispose to HLH. This systematic review aims to characterize HLH in patients with IEInotFHL, especially those in pediatric age. In fact, since the first diagnostic and therapeutic steps for HLH are often taken in the general pediatric setting, pediatricians should be aware of the existence of possible underlying IEI beyond FHL to minimize the potentially fatal risks associated with a missed diagnosis.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (3). The study protocol was registered as PROSPERO CRD42022371425.

Abbreviations: HLH, Hemophagocytic Lymphohistiocytosis; FHL, Familial Hemophagocytic Lymphohistiocytosis; IEI, Inborn Errors of Immunity; ESID, European Society for Immunodeficiencies.

Definitions

IEI: 485 inherited disorders, often due to mutations in a single gene, involving specific impairment of normal development and immune function. IUIS2022 Classification groups IEI into 9 major categories and multiple subgroups based on which part of immune system is impaired (see Supplemental Data for complete classification) (2). IUIS2022 Classification also considers an additional group for phenocopies of IEI.

FHL: IEI which share HLH as their predominant clinical feature. According to IUIS 2022 Classification FHL can be distinguished in two subgroups based on the presence of hypopigmentation. The first subgroup includes pathogenic variants in PRF1, STX1, UNC13D, STXBP2, FAAP24, SLC7A7, and RHOG, while the second subgroup consists of gene variants associated with Chediak-Higashi syndrome, Griscelli type 2, and, less commonly, Hermansky-Pudlak syndrome types 2 and 10, in addition to the neofunction of CEBPE.

IEInotFHL: IEI not belonging to FHL subgroups according to IUIS 2022 Classification.

Study design and search strategy

On 30th September 2022 an extensive search for publications on HLH associated to IEInotFHL was conducted on PubMed, MEDLINE, EMBASE, and Cochrane Central databases (see Supplementary Data for strings). The search string included IEInotFHL previously described as possibly associated to HLH (4–6) and Epstein-Barr Virus (EBV) susceptibility disorders that are not comprised in FHL subgroups according to IUIS 2022 Classification (2). Reference lists were hand-searched for further relevant studies.

Study eligibility and quality assessment

After duplicates were removed through Rayyan online database (7), screening on title and abstract was conducted by three independent reviewers (W.M.S, S.R and M.F). Discrepancies were discussed until a common decision was reached.

A study was considered eligible when the following criteria were met: at least 5 diagnostic criteria of HLH (8), confirmed diagnosis or

high suspicion of IEInotFHL according to IUIS Classification 2022, clinical data report. Records were excluded if they did not describe IEInotFHL, described animal experiments, contained no clinical data, or were not peer reviewed. Phenocopies of IEI were not considered. Non-English records were finally excluded for practical purposes. Quality assessment was performed with Critical Appraisal Tools of the Johanna Briggs Institute (JBI) by two independent reviewers (W.M.S and S.R) (9, 10). No records were excluded because of methodological quality.

Data extraction, synthesis of results and analysis

All data were extracted by a reviewer (W.M.S) using a Microsoft® Excel® spreadsheet developed by the author team and verified by a second reviewer (S.R.). Common decision was to extract the worst laboratory values. The main characteristics of the included studies have been analyzed and summarized in tables. Quantitative variables are expressed as mean and standard deviations (DS) or median and interquartile range (IQR). GraphPad® Prism 9 was used for statistical analysis. Mann-Whitney test was used to compare non-normal values. Fisher and $\chi 2$ tests were used to evaluate differences between groups. The level of significance was set to $p<0.05$.

Results

Study selection

This review included 108 studies (Figure 1) for a total of 178 patients (4, 5, 11–116). Through database search and reference lists screening, 4570 records were identified. After 1304 duplicates were removed, 3263 titles/abstracts were screened and subsequently, 261 full-text articles were assessed for eligibility. All details are shown in Figure 1.

Demographics

At HLH onset, 159/178 patients (89%) were aged 0-18 years, 7/159 pediatric patients (4%) experienced HLH within first 30 days of life (IQR 9-23.5 days) (19, 41, 61, 63, 92, 95, 110) and one of them during fetal life (55). The median age at HLH diagnosis, considering only pediatric patients, was 17.5 months (IQR 4-60 months).

Gender was declared or deductible from genetic diagnosis for 149/178 patients (84%) with a M:F ratio 3:1. As expected, gender ratio varied across distinct IEI groups, according with the inheritance pattern. When excluding all X-linked defects, the M:F ratio was established to 1.5:1. Consanguinity between parents was reported in 28/178 patients (16%) while familiarity for IEI or sudden infant death was reported in 30/178 patients (17%).

HLH in IEInotFHL

The frequencies of HLH diagnostic criteria in selected patients are shown in Table 1.

Genetic diagnosis of IEI was available for 149/178 patients (84%) and causative mutations were reported for 115/149 patients (77%). Precise characterization of the genetic investigations has been challenging due to incomplete data and a lack of information regarding the specific timing of these analyses. For the remaining 16% of cases, the diagnosis of IEInotFHL was established without genetic analysis but relied on criteria defined by ESID (European

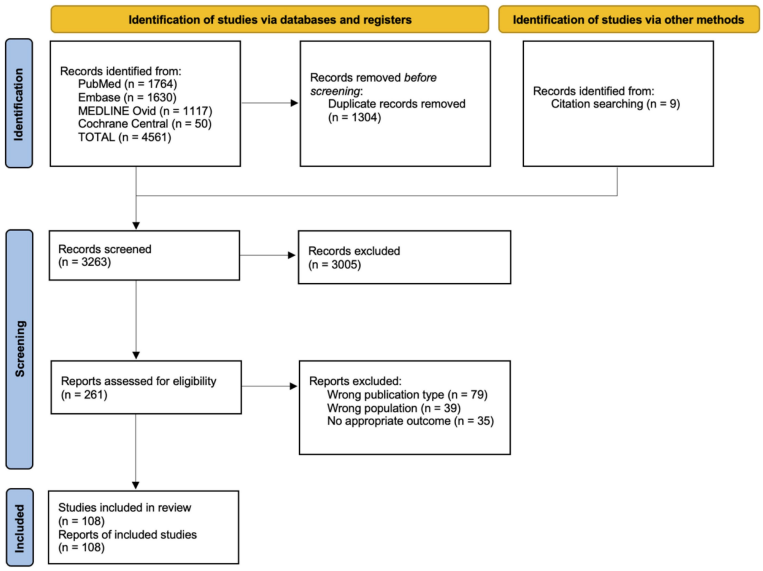

FIGURE 1
Selected reports flow-chart according to PRISMA Guidelines.

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TABLE 1 Clinical and Laboratory data of patients with HLH and IEInotFHL.

HLH-2004 criteria	Prevalence
Fever	171/178 (96.06%)
Splenomegaly	163/178 (91.57%)
Ferritin ≥ 500 μg/L	168/168 (100%)
sIL2R ≥ 2400 U/mL	64/78 (82.05%)
Fibrinogen ≤ 150 mg/dL	98/129 (75.96%)
Triglycerides ≥ 265 mg/dL	126/145 (86.89%)
Cytopenia 2/3 cell lines	153/178 (85.95%)
Hemoglobin ≤9 g/dL (or ≤10 g/dL in first 4 weeks)	108/116 (93.10%)
Neutrophils ≤ 1000/μL	42/83 (50.60%)
Platelets ≤ 100000/μL	113/125 (90.40%)
Hemophagocytosis in bone marrow, liver, spleen	103/137 (75.18%)
Reduced NK cytotoxicity	26/44 (59.09%)
Laboratory	*Median values and IQR [data available]*
Ferritin (μg/L)	4847 (1957.75 20816) [168/178]
sIL2R (U/mL)	4209.4 (2626.25 9645.56) [168/178]
Fibrinogen (mg/dL)	120 (90 170) [129/178]
Triglycerides (mg/dL)	364.5 (290 534.5) [145/178]
Hemoglobin (g/dL)	7.7 (6.7 8.7) [116/178]
Neutrophils (cell//μL)	1240 (360 2530) [83/178]
Platelets (cell//μL)	37500 (19750 71000) [125/178]
ALT (U/L)	301.5 (100.3 614) [54/178]
Albumin (g/dL)	2.3 (2.1 2.4) [12/178]
Total Bilirubin (mg/dL)	1.6 (0.96 4.3) [19/178]
Direct Bilirubin (mg/dL)	1.3 (0.73 2.93) [13/178]
D-dimer (mg/L)	5360 (1113 10520) [10/178]
INR	1.67 (1.48 2.10) [21/178]
LDH (U/L)	1366.5 (738.5 3247) [39/178]
CXCL9 (pg/mL)	27292 (19776 75153.5) [4/178]
Serum IgG (mg/dL)	480 (235 1075) [47/178]
Serum IgA (mg/dL)	100.5 (30.3 158.3) [46/178]
Serum IgM (mg/dL)	53.5 (18.8 181.8) [46/178]
Serum IgE (KU/L)	72.5 (27.5 226.3) [14/178]
CD3+ (cell//μL)	534 (17 1729) [32/178]
CD3+CD4+ (cell//μL)	325 (21 1302) [31/178]
CD3+CD8+ (cell//μL)	482 (9 1452) [29/178]
CD19+ (cell//μL)	343 (19 1071) [38/178]
CD56+CD16+ (cell//μL)	92.5 (10 289) [32/178]

Society for Immunodeficiencies) based on medical history, clinical presentation, and functional laboratory parameters (117). However, for other IEInotFHL, such as those related to innate immunity (12/12 patients, 100%) and autoinflammatory disorders (23/24 patients, 96%), specific diagnosis was only possible through genetic analysis. Otherwise, these conditions would have remained undiagnosed due to the absence of decisive functional tests.

Data collection identified 46 different IEI complicated by HLH at the onset or during disease course (See Supplementary Data for complete list). All IUIS 2022 IEI major groups were represented, apart from complement defects (Figure 2). Most HLH cases identified belonged to groups of IEI affecting both cellular and humoral immunity (45/178, 25%), immune dysregulation disorders (39/178, 22%), defects of phagocyte number or function (30/178, 17%), and defects of intrinsic and innate immunity (24/178, 13%). Recurrence of HLH was reported in 21/178 patients (12%), mainly in intrinsic and innate immunity defects (7/24 vs 14/154, p=0.0048). The distribution of Groups and Subgroups of IEInotFHL is shown in Figure 2, according to IUIS 2022 classification (2). (See Supplementary Data for complete list of identified IEInotFHL).

HLH as first sign of IEInotFHL

The age of HLH onset in the different immune defects are detailed in Figure 2. Predominantly antibody deficiencies presented with HLH at an older age than all the other groups of IEI (mean values 207.9 ± 203.42 vs 67.64 ± 101.04 months; p=0.0039) while patients with SCID showed the earliest onset of HLH compared to all the other subgroups of IEI (mean values 8.22 ± 12.16 vs 87.04 ± 119.46 months; p<0.0001).

Temporal relation between HLH and IEI diagnosis was available for 172/178 patients (97%). In 127/172 patients (74%) HLH preceded IEI diagnosis. However, when evaluating the medical history prior to the HLH event (available for 98/172 patients; 57%), a history of infections could be identified in 38/127 patients (30%), and in 15/127 (12%) at multiple sites. The most frequent infections were pneumonia 17/127 (13%), recurrent in more than half of the cases (59%), upper respiratory tract infections 11/127 (9%), acute otitis media 7/127 (6%), chronic or recurrent sinusitis 4/127 (3%), sepsis 4/127 (3%), chronic/recurrent muco-cutaneous candidiasis 4/127 (3%), skin or visceral abscesses 3/127 (2%), severe skin infections 2/127 (2%), live strain vaccine viral infections 2/127 (2%), meningoencephalitis and osteomyelitis 1/127 each (1%).

Furthermore, other non-infectious signs or symptoms suggestive of IEI were reported prior to the first episodes of HLH. This included failure to thrive in 10/127 patients (8%) or chronic/recurrent bloody or watery diarrhea in 8/127 patients (6%). One patient was previously suspected for Inflammatory Bowel Disease (IBD) (73). Facial dysmorphisms were described in 5/127 patients (4%) while hematologic anomalies such as persistent/recurrent cytopenia or splenomegaly in 13/127 patients (10%). Additionally, a history of hypogammaglobulinemia was reported in 3/127 patients (2%), although in one case it was likely due to nephrotic syndrome (40, 96, 98). Despite available data are limited, 20/127

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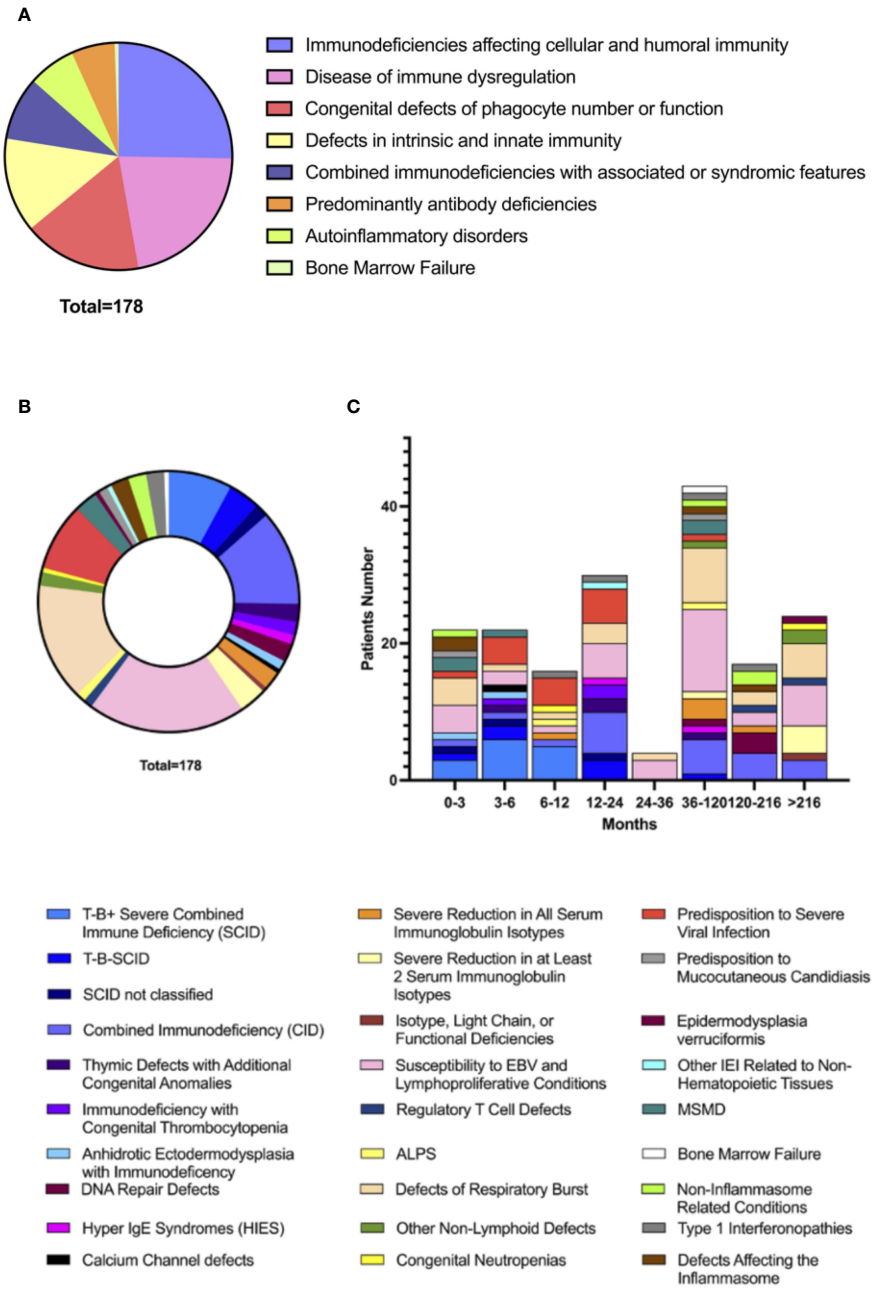

FIGURE 2
Distribution of HLH in Groups **(A)** of IEInotFHL and Subgroups **(B)** of IEInotFHL according with IUIS 2022 Classification of IEI and distribution of subgroup according to age **(C)**.

patients (16%) had silent clinical history before HLH (See Supplementary Data for detailed clinical data).

HLH laboratory data

Laboratory data referred to each group of IEI according to IUIS 2022 Classification are extensively detailed in the Supplement. No significant differences were found among groups of IEI neither in ferritin values, nor in triglycerides, fibrinogen, hemoglobin, and platelets values (Table 1). Conversely, patients with IEI affecting both cellular and humoral immunity had significantly lower sIL2R values than all the other IEInotFHL (mean values 2407.25 ± 1467.54 U/mL vs 8015.04 ± 7049.91 U/mL; p=0.0012). Moreover, patients with defects of intrinsic or innate immunity had significantly higher values of neutrophils (mean values 8448 ± 7818 cell/μL vs 1960± 3266cell/μL; p<0.0001) and aspartate aminotransferase (mean values 3831 ± 4855 U/L vs 1188 ± 2015 U/L; p=0.0273) than all other IEInotFHL. Additional laboratory data are listed in Table 1.

Triggers and clinical signs at onset of HLH

Infectious triggers were reported in 121/178 patients (68%). Multiple concomitant triggers were identified in 21/178 patients (12%). EBV, alone or combined with other pathogens, was found in 48/178 patients (27%), and it was the most frequent trigger of HLH in most groups of IEI (Figure 3). However, in 4 patients included in the "susceptibility to EBV and lymphoproliferative disorders" subgroup, HLH was triggered by different viruses (Parvovirus, HHV8, and CMV) (20, 61, 68). Additionally, in 12 patients within the same subgroup a trigger could not be clearly identified after EBV infection was ruled out.

HLH was infrequently triggered by infections in patients with IEI classified as autoinflammatory disorders (e.g., type 1 interferonopathies or defects affecting the inflammasome) when compared to all the others (1/12 vs 120/166, p<0.0001) (25). Selective triggers were identified for specific IEI: fungal infections were more frequent in patients with defects of phagocyte number or function (5/25 vs 5/96, p=0.0167) while BCG was more commonly found in patients with intrinsic or innate immunity disorders (5/19 vs 3/102, p=0.0024). Leishmania was identified only in patients with CGD (3 X-linked and 1 AR-CGD) (4, 62) while live-strain viral vaccine were only in patients with intrinsic or innate immunity disorders (21, 53, 103).

Regardless of infectious trigger, airways were the most frequent site of infection with symptomatic presentation such as cough or dyspnea. Respiratory signs were followed by skin rash (30/178, 17%) and gastrointestinal signs (25/178, 14%). Neurologic signs as consciousness impairment, seizures, ataxia, or focal signs were reported in 21/178 patients (12%) at onset of HLH. Nevertheless, Central Nervous System (CNS) involvement was confirmed by lumbar puncture or brain Magnetic Resonance Imaging (MRI) in 5/21 patients (24%) and 7/21 patients (33%), respectively. Overall, liver involvement, inclusively considering hepatomegaly and transaminases above 100 U/L, was reported in 97/178 patients (54%), while jaundice and liver failure were reported in 5/178 (3%) (30, 38, 63, 70, 80) and 3/178 patients (2%) (45, 61, 80), respectively.

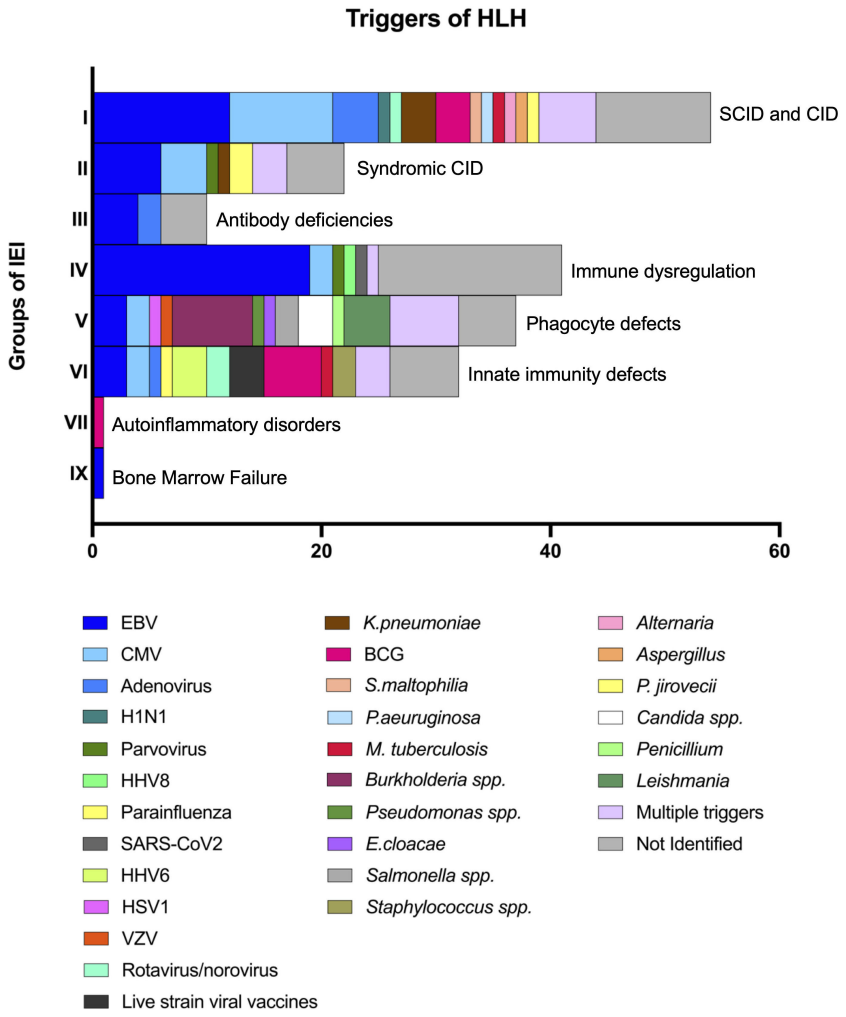

FIGURE 3
Triggers of HLH in patients with underlying IEInotFHL.

Treatment and outcome of HLH in IEInotFHL

Treatment data were available for 157/178 patients (88%) and are listed in Table 2. HLH-94/04 protocol was set up in 63/157 patients (40%), whereas 21/157 patients (13%) received corticosteroids only, which alone provided resolution in 12/21 patients (57%).

Biologic agents or immunosuppressive therapies, as shown in Table 2, were used in addition to complete HLH treatment protocol in 8/157 patients (5%) and used as an alternative approach to delay chemotherapy with VP16 in 22/157 patients (14%). Finally, at the time of reports submission, 32/178 patients (18%) underwent Hematopoietic Stem Cell Transplantation (HSCT). More specific details regarding transplantation could not be provided because data were incomplete. Information about type of donor and conditioning regimen were reported for only 14/32 patients (44%) and 13/32 patients (41%), respectively.

Outcome was clearly described for 171/178 patients (96%). At the time of reports submission 84/171 patients (49%) were alive. Age at death was clearly described for 43/171 patients (25%). The leading cause of death were multiorgan failure (22/47, 47%), respiratory failure (16/47, 34%), and sepsis (7/47, 15%). Outcome was significantly worse when the onset of HLH was in the first 12 months (36/57 vs 51/114 patients dead, p=0.0231). Overall mortality was significantly higher among patients with IEI affecting cellular and humoral immunity (CID and SCID) compared to all the other IEI (38/60 vs 49/111 patients dead, p=0.0166). After HSCT, 13/32 patients (41%) died (mean of 57.9 ± 95.8 days). No differences in survival outcome were found between transplanted and not transplanted patients (13/32 vs 74/139 patients dead, p=0.1982). No significative differences were also found between patients with or without CNS involvement (15/25 vs 72/146 patients dead, p=0.3234), or between patients who received etoposide and the ones who did not (35/60 vs 52/111 patients dead, p=0.1516).

TABLE 2 Treatment of HLH in patients with IEInotFHL.

Treatment	N of patients
HLH-94/04 protocol	63/157 (40.12%)
Corticosteroids only	21/157 (13.37%)
Specific Treatment	N of patients
Antimicrobial Antibiotic Antiviral Antifungal/antiparasitic	58/157 (36.94%) 45/157 (28.66%) 18/157 (11.46%) 17/157 (10.82%)
Corticosteroids Dexamethasone MDP Other/not specified	133/157 (84.71%) 97/157 (61.78%) 22/157 (14.01%) 19/157 (12.10%)
VP16 (Etoposide)	63/157 (40.12%)
Cyclosporine	61/157 (38.85%)
Anakinra	11/157 (7%)
Rituximab	12/157 (7.64%)
Emapalumab	4/157 (2.54%)
Etanercept	2/157 (1.27%)
Azathioprine	2/157 (1.27%)
Sirolimus	2/157 (1.27%)
Ruxolitinib	2/157 (1.27%)
Basiliximab	1/157 (0.63%)
Infliximab	1/157 (0.63%)

Discussion

Characterization of HLH as a possible clinical manifestation of an underlying IEI is critical to properly manage this life-threatening condition. Moreover, raising awareness among pediatricians and neonatal/pediatric intensivists, who often deal with HLH at onset, is crucial to ensure rapid recognition, appropriate treatment of any underlying IEI, and improved outcomes both during HLH and, even more so, after its remission.

Chinn et al. in 2018 highlighted significant genetic diversity within patients meeting HLH criteria (118). Among 122 subjects enrolled over a 17-year period, genetic testing was conducted on 101 subjects. Notably, whole-exome sequencing (WES) analysis identified IEInotFHL in 14 cases and dysregulated immune activation or proliferation disorders in 8 cases. However, it has long been known that IEInotFHL can predispose to the development of HLH. In 2015 a large survey and literature review on patients with HLH and IEI other than FHL or XLP performed by Bode et al. found that combined immunodeficiencies (CID and SCID) and chronic granulomatous disease (CGD) were the most frequent underlying IEInotFHL (4). Similar conclusions were obtained by Cetinkaya et al. in another single-center study enrolling 28 patients with HLH, between the years 2013 and 2017, in which combined immunodeficiencies represented the most frequent IEInotFHL (5).

In accordance with previous reports (4, 5), we noticed that most cases of HLH occurred in the groups of SCID and CID, in the group of immune dysregulation disorders such as XLP-1 and XLP-2, and in CGD patients. However, all groups in the IUIS classification except complement deficiencies were found to underlie HLH development. Specifically, 46 different IEIs were identified in patients with HLH in this review.

Recognizing the methodology limitation of a systematic review, we acknowledge its non-quantitative nature, impeding the determination of individual IEInotFHL prevalence. Notably, the exclusion of numerous studies exploring the association between EBV susceptibility disorders (e.g., XLP1 or XLP2) and HLH (119–121) was guided by our specific criteria. This exclusion may have potentially led to an underestimation of the significance of each IEInotFHL, especially the well-established EBV susceptibility disorders. Indeed, Gadoury-Levesque et al. proposed that SAP and XIAP deficiency contribute to approximately 15% of genetically confirmed HLH disorders (122). This prevalence

aligns with the combination of HLH susceptibility with pigmentary defects and is slightly lower than each of the three common FHL disorders, as indicated by the same study.

Nevertheless, we believe that focusing only on FHL or EBV susceptibility disorders in patients with HLH might be reductive and lead to missed diagnoses of other IEI resulting in increased numbers of complications, sequelae, or death in undiagnosed patients. Therefore, these results suggest that specific functional tests beyond flow cytometric assessment of perforin and NK degranulation activity should be included in first diagnostic steps in all patients, followed by extensive genetic analysis not limited to FHL solely. Genetic investigations, ranging from basic to more in-depth testing, were performed in over 80% of cases, being decisive especially in cohorts of IEInotFHL such as autoinflammatory disorders or innate immunity defects, wherein non-genetic testing was inconclusive. These observations underscore the pivotal role of genetics in discerning intricate immune-related conditions when suspicion is elevated, and conventional immunological assessments remain inconclusive. Additionally, in line with the suggestions of Chinn et al. (118), these findings emphasize the constraints of targeted FHL gene sequencing for the majority of HLH patients, while accentuating the potential of WES to precisely identify other IEI and pinpoint specific therapeutic approaches.

Bode et al. demonstrated that HLH was the initial presentation of IEI in 57% of patients (4). Similar conclusions were obtained by Cetinkaya et al (5). In the present review HLH episodes preceded the diagnosis of IEI in three quarters of patients, often as the first manifestation of the underlying disease. This was also true for SCID, which are usually suspected in first months of life because of severe life-threatening infections. Therefore, it can be speculated that widespread implementation of newborn screening for SCID may also serve as a preventive measure against potentially life-threatening HLH episodes triggered by infections (123–125). On the other hand, a previous history of susceptibility to recurrent or severe infections was reported in one-third of cases diagnosed with IEInotFHL after HLH, but these infections were probably not considered relevant enough to prompt a suspicion of IEI.

The application of clinical screening based on the 10 Jeffrey Modell Foundations warning signs based on infectious disease susceptibility, has greatly promoted knowledge of immunodeficiencies in the last decades. Nevertheless the International Immunology Network emphasized the importance of inflammatory and autoimmune manifestations among the warning signs to reduce the missed diagnoses of IEI (126). In this regard it could be useful to consider HLH as a possible warning sign for IEI and include it among the many outlined by the Jeffrey Modell Foundation.

The present review showed that HLH triggers usually reflect the specific susceptibility to infections of different groups of IEI. Fungal triggers indeed, were more represented among patients with underlying defects of phagocyte number and function while live strain vaccines like BCG were among patients with specific disorders of innate immunity like mendelian susceptibilities to mycobacterial disease. These data reinforce the theory that HLH is often a state of "immune frustration" due to the inability of the immune system to efficiently fight infection and achieve complete clearance or control of the pathogen resulting in a self-sustaining cycle of antigenic stimulation and hyperinflammation. The identification of specific pathogens in the context of an episode of HLH could help direct clinical suspicion to a specific underlying IEInotFHL. For instance, CGD should always be investigated after the identification of *Leishmania* spp., *Candida* spp. or *Burkholderia* spp. in HLH patients, even more so if they have recurrent or persistent HLH. Anyway, in accordance with the literature, viruses were the primary triggers of HLH in almost all groups of IEInotFHL (127). Other viruses were also identified as triggers in patients with EBV-related disorders, as well as EBV was the trigger even in non-EBV-related disorders. Therefore, infectious workup should be as wide as possible and not limited to the detection of EBV.

Regardless of the infectious trigger, children with IEInotFHL may develop HLH in the context of respiratory or gastrointestinal infections more frequently (25%) than those with FHL who rarely show signs of infection at the onset of HLH (128). In contrast to the inflammatory phenotype, liver and CNS involvement was reported more rarely in patients with HLH and underlying IEInotFHL than in FHL, where CNS involvement ranges from 30% to 73% of cases and implies a worse outcome, as confirmed by Amirifar et al (129, 130).

Comparison of data from this review with those in the literature found no significant differences in routine diagnostic markers of HLH compared with secondary HLH or FHL.

Regarding treatment, the data obtained from this review are uneven and not based on long follow-up, making them inconsistent for speculations on therapeutic efficacy in the different IEI groups. However, as expected in view of the high infectious risk, less than half of patients received HLH-1994 or HLH-2004 treatment with chemotherapy. This may partly be attributed to the identification of specific pathogens as trigger of HLH which prompted clinicians to immediately start targeted antimicrobial treatment and delay the application of chemotherapy. In two cases, this approach resolved HLH without additional treatments (32, 47).

Acknowledging the partial limitations of the data, it is critical to point out that the results of chemotherapy were not significantly better. While FHL is a more uniform category, HLH due to IEInotFHL requires subcategorization for tailored therapy, as it does not always involve T-cell activation. In fact, in the North American Consortium for Histiocytosis (NACHO) recommendations, Jordan et al. introduced the term "HLH disease mimics" to refer to all those conditions that, while meeting HLH criteria, would not benefit from immunosuppression (131). Based on the observations from this systematic review, some HLH due to IEInotFHL might actually meet this definition. Thus, although data should be interpreted with caution due to potential sources of bias, our suggestion is that patients with IEInonFHL may not necessarily require comprehensive treatment protocols for HLH.

Therefore, cautious evaluation and monitoring, along with individualized treatment strategies based on underlying IEInotFHL or identified triggers, remain mandatory.

In addition, pathway-specific target therapies are progressively gaining more space in the treatment of HLH at the expense of broad-spectrum etoposide-based chemotherapy, especially for patients with IEI, both because of a better understanding of individual pathogenetic defects (e.g., defects in interferon pathways) and because of greater availability of new molecules that necessarily exert a less global immunosuppressive effect.

Although the overall outcomes did not appear to be significantly influenced by HSCT, it is important to note that these findings should be interpreted with caution due to the lack of long-term follow-up data and insufficient details on conditioning regimens and prophylaxis of graft-versus-host disease (GVHD) in the selected studies. Further research and comprehensive analysis are needed to provide a more conclusive understanding of the impact of treatments and outcomes of HLH in the context of IEI.

The main limitation of this work is the retrospective design of the study which does not allow conclusions about significant differences in laboratory features for specific IEIs or treatment approaches that are often not well described.

Conclusions

HLH represents a significant and unpredictable clinical challenge for pediatricians and pediatric intensivists who often manage this clinical emergency at its onset. To the best of our knowledge this is the first systematic review about HLH and IEI other than FHL. The data presented within this study suggest that HLH could potentially emerge as a clinical hallmark across various forms of IEInotFHL, often serving as their initial recognizable indicator. Proficiency in discerning HLH indicators and, notably, uncovering the etiology of this potentially fatal condition can notably enhance patient prognoses, extending benefits even beyond HLH remission. The recognition that early detection of underlying genetic origins can reshape patient management in next future is evident. As the genetic landscape unfolds, an appealing transition to personalized approaches emerges, enriching therapeutic options and directing us toward precision interventions, ultimately leading to improved patient outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

SR: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. WS: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. LL: Writing – review & editing. CC: Writing – review & editing. FL: Writing – review & editing. DD: Writing – review & editing. MF: Writing – review & editing. LP: Writing – review & editing. ES: Supervision, Validation, Writing – review & editing. GI: Supervision, Validation, Writing – review & editing. MR: Supervision, Validation, Writing – review & editing. CA: Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1282804/full#supplementary-material

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