

Clinical Manifestations and Immunologic Features of Chediak–Higashi Syndrome: A 12-Year National Registry Study from Iran

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Abstract

Introduction

Chediak–Higashi syndrome (CHS) is a rare autosomal recessive inborn error of immunity caused by biallelic mutations in the *LYST* gene. Population-based data on its clinical and immunological features remain scarce, particularly from Middle Eastern populations. We aimed to characterize the clinical manifestations, immunological findings, and outcomes of patients with CHS registered in the Iranian Primary Immunodeficiency Registry (IPIDR).

Methods

This retrospective cohort study included all patients with a confirmed diagnosis of CHS registered in the IPIDR between 2011 and 2023. Demographic, clinical, laboratory, and immunological data were extracted from registry records. Diagnosis was established based on cytological and/or molecular criteria. Data are presented using descriptive statistics.

Results

23 patients with confirmed CHS were included. The median age at data extraction was 216 months (IQR: 168–363). The median age at symptom onset was 12 months (IQR: 6.5–18) and at diagnosis 24 months (IQR: 12–48), yielding a median diagnostic delay of 5.8 months (IQR: 1.75–23.25). Parental consanguinity was present in 18 patients (78.3%), and 14 patients (60.9%) were male. At final follow-up, 21 patients (91.3%) were alive, one (4.3%) had died from sepsis, and the status of one (4.3%) was unknown. The most common clinical features were recurrent respiratory and skin infections, partial oculocutaneous albinism, silvery hair, nystagmus, hepatosplenomegaly, and pancytopenia.

Conclusion

CHS in Iran presents early and carries a risk of life-threatening complications, underscoring the need for prompt diagnosis and close follow-up. Registry-based data such as those from the IPIDR are essential for characterizing ultra-rare disorders and informing clinical practice. Early genetic screening in high-risk families and timely HSCT referral before the accelerated phase develops should be prioritized.

1. Introduction

Chediak–Higashi syndrome (CHS) is a rare autosomal recessive inborn error of immunity caused by biallelic mutations in the lysosomal trafficking regulator (*LYST*) gene (1). Loss of *LYST* function impairs intracellular vesicle dynamics, causing the abnormal accumulation of giant cytoplasmic granules in leukocytes and other secretory cells (2). Clinically, the disorder presents with partial oculocutaneous

albinism, recurrent pyogenic infections, a bleeding tendency, and variable neurological features including peripheral neuropathy and ataxia (3, 4). Affected individuals exhibit impaired neutrophil chemotaxis and bactericidal activity, reduced NK cell cytotoxicity, and defective degranulation of cytotoxic lymphocytes, rendering them highly susceptible to severe bacterial and viral infections (5). A particularly dangerous complication is the accelerated phase, a hyperinflammatory state closely resembling hemophagocytic lymphohistiocytosis (HLH), which develops in a substantial proportion of patients with classic CHS and is a leading cause of morbidity and mortality in affected children (6).

Despite being described more than seven decades ago, CHS remains poorly understood at the population level. Its extreme rarity and phenotypic variability have limited most published evidence to isolated case reports and small case series (5, 7). Diagnosis is frequently delayed, particularly in settings where molecular testing and functional immunologic assays are not readily accessible (8). Data from Middle Eastern populations are especially sparse, and registry-based cohort studies from this region are virtually absent.

National registries for inborn errors of immunity provide a critical infrastructure for characterizing rare disorders that cannot be adequately studied through conventional study designs. The Iranian Primary Immunodeficiency Registry (IPIDR) systematically captures demographic, clinical, laboratory, and outcome data from patients across Iran, offering a unique platform for such analyses.

In this retrospective cohort study, we examined the clinical manifestations, immunologic findings, and outcomes of patients with confirmed CHS enrolled in the IPIDR between 2011 and 2023. We aimed to characterize the clinical and immunologic spectrum of CHS in Iran and to provide regional data that may support earlier recognition and better management of this disorder.

2. Methods

2.1 Study Design and Setting

This was a retrospective registry-based cohort study of patients with confirmed CHS enrolled in the Iranian Primary Immunodeficiency Registry (IPIDR). The IPIDR is a national registry that systematically documents patients with inborn errors of immunity from tertiary referral centers and university-affiliated hospitals across Iran. Data are recorded prospectively during routine clinical follow-up using standardized entry forms.

For this analysis, registry records of patients diagnosed with CHS between April 2011 and March 2023 were reviewed. Follow-up was defined from the date of diagnosis to the last documented clinical visit, death, or loss to follow-up.

2.2 Study Population

All patients with a confirmed diagnosis of CHS registered in the IPIDR between April 2011 and March 2023 were eligible for inclusion. Diagnosis was established according to the European Society for

Immunodeficiencies (ESID) criteria, requiring the presence of characteristic cytological findings, notably giant intracytoplasmic granules in peripheral blood leukocytes, and/or identification of pathogenic or likely pathogenic variants in the *LYST* gene.

All eligible patients were included regardless of age, sex, or disease severity. Patients were excluded if the diagnosis was unconfirmed, if registry records lacked essential demographic or clinical data, or if they were registered outside the study period. Duplicate entries were identified and resolved through cross-referencing of demographic and clinical information. A total of 23 patients met the inclusion criteria and were included in the final analysis.

2.3 Data Collection

Data were extracted from the IPIDR using a structured data extraction form developed for this study. Collected variables were categorized into three domains: demographic, clinical, and laboratory/immunological.

Demographic variables included age, sex, parental consanguinity, family history of immunodeficiency, and survival status at the time of data extraction. Clinical variables comprised age at symptom onset, age at diagnosis, diagnostic delay, initial presenting symptoms, history of recurrent or severe infections, dermatological and neurological manifestations, organomegaly, cytopenias, and occurrence of the accelerated phase. Laboratory and immunological variables included complete blood count parameters, hepatic enzymes, serum protein concentrations, immunoglobulin levels, lymphocyte subset distributions, and results of functional immune assays and *LYST* gene analysis where available.

All variables were extracted directly from registry records. Where data were missing or unavailable, the affected variables were excluded from the respective analyses.

2.4 Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables are reported as frequencies and percentages. Variables with incomplete data were analyzed based on available records.

2.5 Ethical Approval

This study was approved by the Ethics Committee of Abadan University of Medical Sciences, Abadan, Iran (approval code: IR.ABADANUMS.REC.1402.169) and conducted in accordance with the Declaration of Helsinki.

3. Results

3.1 Demographic and Baseline Clinical Characteristics

A total of 23 patients with confirmed CHS were included in the analysis. Demographic and baseline clinical characteristics are shown in Table 1.

The median age at data extraction was 216 months (IQR: 168–363). The median age at symptom onset was 12 months (IQR: 6.5–18) and the median age at diagnosis was 24 months (IQR: 12–48), yielding a median diagnostic delay of 5.8 months (IQR: 1.75–23.25). The cohort included 14 male (60.9%) and 9 female (39.1%) patients. Parental consanguinity was reported in 18 patients (78.3%). No family history of immunodeficiency was documented in any patient. At the time of data extraction, 21 patients (91.3%) were alive, one (4.3%) had died from sepsis, and the survival status of one patient (4.3%) was unknown.

Table 1. Demographic and Clinical Characteristics of the Studied Patients.

Parameter	Statistical Index	Results
Current age (months)	Median (interquartile range)	216 - (168–363)
Age at disease onset (*DOO) (months)	Median	12 - (5.6–18)
Age at disease diagnosis (**DOD) (months)	Median	24 - (12–48)
Diagnostic delay (months)	Median	5.8 - (1.75–23.25)
Anemia	Number (percentage)	18 - (78.3%)
Sex (female/male)	Number	Female: 9 (39.1%), Male: 14 (60.9%)
Survival status (deceased / alive / unknown)	Number	Alive: 21 (91.3%), Deceased: 1 (4.3%), Unknown: 1 (4.3%)

*DOO: Date of Onset (age at disease onset)

**DOD: Date of Diagnosis (age at disease diagnosis)

3.2 Hematological, Biochemical, and Immunological Findings

Hematological, biochemical, and immunological findings are shown in Table 2. The median WBC count was 4,300 cells/mm³ (IQR: 3,080–8,210), with a median lymphocyte proportion of 60.0% (IQR: 44.5–72.75) and a median neutrophil proportion of 21.0% (IQR: 12.0–32.0). Median hemoglobin was 9.2 g/dL (IQR: 8.9–11.5) and median platelet count was 125,000/μL (IQR: 81,000–304,500).

Hepatic enzyme levels were elevated across the cohort. Median AST was 45 U/L (IQR: 33–208), median ALT was 36 U/L (IQR: 19–90), and median ALP was 377 U/L (IQR: 100.75–1,072.25). Median total protein was 5.9 g/dL, median albumin was 3.26 g/dL (IQR: 2.715–3.825), and median globulin was 3.2 g/dL.

Immunological assessment showed a median CD3⁺ T-cell percentage of 61.5% (IQR: 55.1–63.6), with median CD4⁺ and CD8⁺ percentages of 25.0% (IQR: 18.9–31.8) and 26.6% (IQR: 22.2–40.5), respectively. CD16⁺ and CD56⁺ NK cell data were not consistently available across patients. Median serum IgG, IgA, IgM, and IgE levels were 1,350 mg/dL (IQR: 677–2,600), 82 mg/dL (IQR: 72–310), 130 mg/dL (IQR: 101–225), and 31 IU/mL, respectively.

Table 2. Laboratory Characteristics of the Studied Population.

Parameter	Statistical Index	Results
WBC (/mm³)	Median (interquartile range)	4300 (3080–8210)
Lymphocytes (%)	Median	60 (44.5–72.72)
Neutrophils (%)	Median	21.4 (12–32)
HB (g/dL)	Median	9.2 (8.9–11.5)
Platelets (/μL)	Median	125,000 (81,000–304,500)
SGOT (U/L)	Median	45 (33–208)
SGPT (U/L)	Median	36 (19–90)
ALP (U/L)	Median	377 (100.75–1072.25)
Total serum protein (g/dL)	Median	5.9 (3.53–NA)
Serum albumin (g/dL)	Median	3.26 (2.715–3.825)
Serum globulin (g/dL)	Median	3.2 (3.2–3.2)
CD3 (%)	Median	61.5 (55.1–63.6)
CD4 (%)	Median	25 (18.9–31.8)
CD8 (%)	Median	26.6 (22.2–40.5)
CD19 (%)	Median	12.1 (4.46–NA)
CD56 (%)	Median	NA
CD16 (%)	Median	NA
CD16/CD56 (%)	Median	7 (7–7)
IgG (mg/dL)	Median	1350 (677–2600)
IgA (mg/dL)	Median	82 (72–310)
IgM (mg/dL)	Median	130 (101–225)
IgE (IU/mL)	Median	31 (9–NA)

Note: NA indicates missing data for the corresponding sample. WBC; White Blood Cells, HB; Hemoglobin, SGOT; Serum Glutamic-Oxaloacetic Transaminase (AST), SGPT; Serum Glutamic-Pyruvic Transaminase (ALT), ALP: Alkaline Phosphatase, CD; Cluster of Differentiation, Ig; Immunoglobulin.

3.3 Clinical Manifestations During the Disease Course

Clinical manifestations recorded throughout the disease course are shown in Table 3 and Figure 1. Enteropathy was the most common finding, identified in 10 patients (43.5%), followed by pneumonia and chronic diarrhea, each present in 9 patients (39.1%). Dyspnea and abscess were each documented in 4 patients (17.4%). Sinusitis and jaundice were each recorded in 3 patients (13.0%). Otitis media, septicemia, candidiasis, and failure to thrive (FTT) were each noted in 2 patients (8.7%). Bronchiectasis and pulmonary crackles were each present in 1 patient (4.3%).

Table 3. Clinical Manifestations of the Studied Patients.

Clinical Manifestation	Number (n)	Percentage (%)
Enteropathy	10	43.5
Pneumonia	9	39.1
Chronic diarrhea	9	39.1
Dyspnea	4	17.4
Abscess	4	17.4
Sinusitis	3	13.0
Jaundice	3	13.0
Ear infection	2	8.7
Allergy	2	8.7
Sepsis	2	8.7
Candidiasis	2	8.7
FTT	2	8.7
Bronchiectasis	1	4.3
Pulmonary crackles	1	4.3

FTT, Failure to thrive.

3.4 Initial Clinical Presentations

Initial clinical presentations at disease onset are shown in Figure 2. Fever was the most common presenting symptom, reported in 14 patients (60.9%). Cough was noted in 5 patients (21.7%) and

recurrent infections in 4 patients (17.4%). Vomiting and pneumonia were each recorded as initial symptoms in 3 patients (13.0%). Chronic diarrhea was the presenting complaint in 2 patients (8.7%). Hepatosplenomegaly, oral candidiasis, furunculosis, and lymphadenopathy were each noted in 1 patient (4.3%).

4. Discussion

This national registry-based cohort provides a systematic characterization of CHS in Iran, demonstrating a predominantly early-onset, multisystemic disease course marked by recurrent infections, cytopenias, and immune dysfunction. Despite its rarity, the clinical and immunological burden was substantial across our cohort, and diagnostic delay remained a consistent challenge. These findings highlight the value of national registries in capturing real-world data on ultra-rare disorders, and point to the need for greater clinical awareness of CHS in regions where such evidence has been absent.

Parental consanguinity was documented in 78.3% of patients, reflecting the autosomal recessive inheritance of CHS and the relatively high prevalence of consanguineous marriage in Iran. Aghamohammadi et al. similarly reported consanguinity as a major contributing factor to inborn errors of immunity in Iran, noting its strong association with autosomal recessive phenotypes across multiple immunodeficiency categories (9). At the regional level, Al-Mousa and Al-Saud demonstrated that consanguinity rates exceeding 50% are consistently observed among patients with autosomal recessive primary immunodeficiencies across Middle Eastern and North African populations, directly amplifying disease incidence in these communities (10). The socioeconomic and cultural factors that sustain these marriage practices in the region further compound disease risk (11), highlighting the need for targeted genetic counseling and family-based screening in affected populations.

Symptoms first appeared at a median age of 12 months, yet a definitive diagnosis was not established until a median of 24 months, yielding a diagnostic delay of 5.8 months. Carneiro et al., in a Brazilian single-center cohort, reported a comparable delay and attributed it primarily to the nonspecific nature of early clinical manifestations, which frequently overlap with common pediatric infectious conditions (6). Gopaal et al. further highlighted that phenotypic overlap between CHS and other primary immunodeficiencies, particularly in cases complicated by Epstein–Barr virus-triggered HLH, can substantially impede timely referral to specialized immunologic services (12). This delay carries real clinical consequences: prolonged diagnostic latency increases cumulative infectious morbidity and raises the risk of accelerated phase onset before curative therapy can be initiated.

More than 90% of patients were alive at final follow-up, suggesting meaningfully improved outcomes compared with historical data, likely reflecting advances in infection management and earlier recognition of disease complications. Nagai et al., in a nationwide Japanese survey, reported that survival in CHS has improved substantially with earlier transplantation and better supportive care, though progression to the accelerated phase remained the dominant cause of death (13). Eapen et al. demonstrated in a multicenter transplantation cohort that hematopoietic stem cell transplantation performed before the

accelerated phase was associated with significantly better long-term survival, while transplantation after HLH onset carried considerably higher mortality (14). These data, combined with our findings, reinforce that early HSCT referral, before the accelerated phase develops, remains the only currently available curative intervention for CHS.

Enteropathy, chronic diarrhea, and pneumonia were the most frequent clinical manifestations, and fever was the predominant initial presenting symptom, followed by respiratory complaints and recurrent infections. Rudramurthy and Lokanatha similarly documented fever as the most common initial presentation in their case series, with a substantial proportion subsequently developing HLH (15). Farhoudi et al., reporting on six Iranian patients with CHS, noted that recurrent infections and oculocutaneous albinism were the most consistent early clinical features, and that hematological abnormalities served as pivotal diagnostic clues once the disease was suspected (16). The consistent predominance of nonspecific early symptoms across these independent series highlights the need for heightened clinical suspicion in any infant presenting with recurrent infections, particularly when accompanied by subtle pigmentary changes or unexplained cytopenias.

Hematological abnormalities — including anemia, neutropenia, and thrombocytopenia — were prevalent and consistent with the recognized hematologic phenotype of CHS. Naamane et al. reported that bi-lineage cytopenias with characteristic giant granules in granulocytes were a hallmark finding, frequently coinciding with early hemophagocytic activity (17), while Roy et al. noted comparable patterns in a tertiary-care series from South India, where cytopenias correlated directly with infectious severity (18). At the mechanistic level, Ganz et al. demonstrated that neutrophils in CHS are deficient in key microbicidal proteins, including cathepsin G and elastase, thereby impairing bactericidal function and contributing to the cycle of recurrent infection and progressive cytopenia (19). Amri et al. further corroborated these findings in a recent Tunisian case, documenting severe cytopenias with giant leukocyte granules reflecting dysfunctional lysosomal trafficking and compromised phagocytic capacity (20). Hematological abnormalities in CHS arise from intrinsic defects in lysosomal trafficking, early hemophagocytic activity, and impaired microbicidal function, a combination that warrants close hematologic monitoring throughout the disease course.

Immunological assessment revealed near-normal lymphocyte counts and largely preserved immunoglobulin levels, yet cytotoxic function was profoundly impaired — consistent with the qualitative rather than quantitative nature of immune dysfunction in CHS. Chiang et al. showed that despite preserved cell numbers, cytotoxic T cells and NK cells exhibit severe defects in lytic granule exocytosis (21), and Gil-Krzewska et al. confirmed that NK cells retain normal cytokine secretion while failing to degranulate effectively due to disrupted LYST-dependent trafficking (22). Sepulveda et al. further demonstrated that loss of functional LYST impairs the biogenesis of secretory lysosomes, resulting in enlarged dysfunctional granules and markedly reduced cytotoxic efficacy despite preserved intracellular perforin and granzyme expression (23). This dissociation between apparently normal lymphocyte counts and severely impaired cytotoxic function has direct diagnostic implications: standard immunological

screening may appear reassuringly normal in CHS, making functional assays essential for accurate disease characterization.

5. Limitations

Several limitations should be considered when interpreting the findings of this study. First, the retrospective registry-based design depended on data recorded during routine clinical practice, which may have resulted in incomplete clinical, laboratory, or immunologic information in some patients. Second, CHS is an ultra-rare inborn error of immunity, and the inherently limited number of affected individuals worldwide constrains the scale of any single-centre or registry-based study. Third, comprehensive molecular analyses and standardized functional immune assays, including NK-cell cytotoxicity and neutrophil chemotaxis testing, were not consistently available for all patients. Finally, long-term outcomes, particularly neurologic progression and post-transplant follow-up, could not be systematically evaluated because of incomplete longitudinal data.

6. Conclusion

CHS in Iran presents as an early-onset, multisystemic disorder with a substantial infectious and hematologic burden, a meaningful diagnostic delay, and a high rate of parental consanguinity. Although survival was favorable in this cohort, the risk of progression to the accelerated phase and life-threatening complications underscores the need for early diagnosis, prompt functional and molecular evaluation, and timely referral for curative therapy. National registries such as the IPIDR provide an essential platform for characterizing ultra-rare disorders and should be leveraged to guide genetic counseling, clinical decision-making, and future prospective studies in this population.

Declarations

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Author Contributions:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Elaheh Karimzadeh-Soureshjani, Samaneh Delavari and Daryoush Kiani-Shamsabadi. The first draft of the manuscript was written by Ali Saeedi-Boroujani, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Financial interests:

The authors declare they have no financial interests.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Abadan University of Medical Sciences (AUMS) (No. IR.ABADANUMS.REC.1402.169).

Consent to participate

Not applicable due to the retrospective design of the study.

Consent for publication: Not applicable.

Clinical trial number: not applicable

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Figures

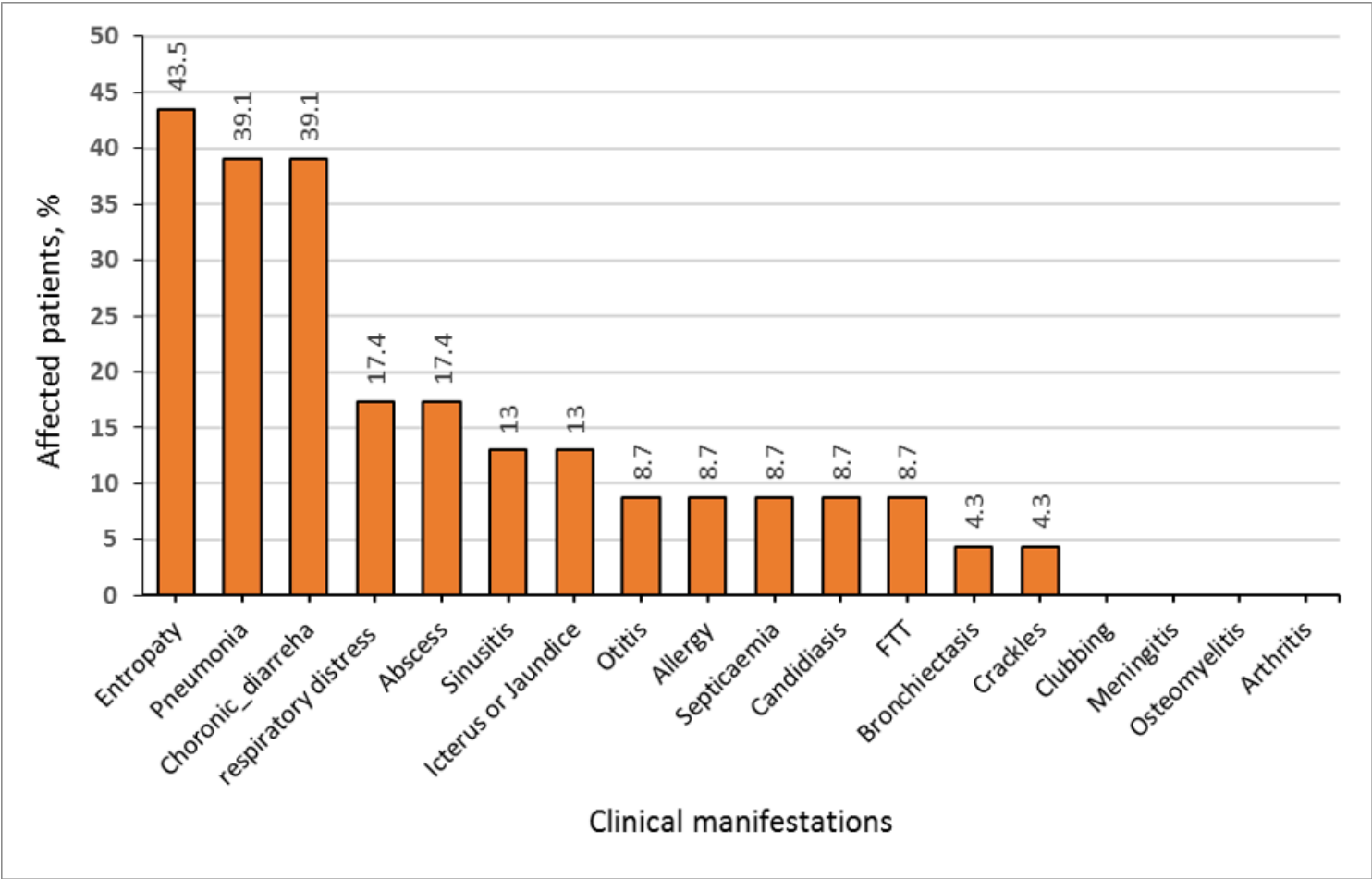


Figure 1

Clinical manifestations recorded during the disease course in patients with CHS (n = 23). Each bar represents the number and percentage of patients with the indicated manifestation at any point during follow-up. Patients may have had more than one manifestation. FTT, failure to thrive.

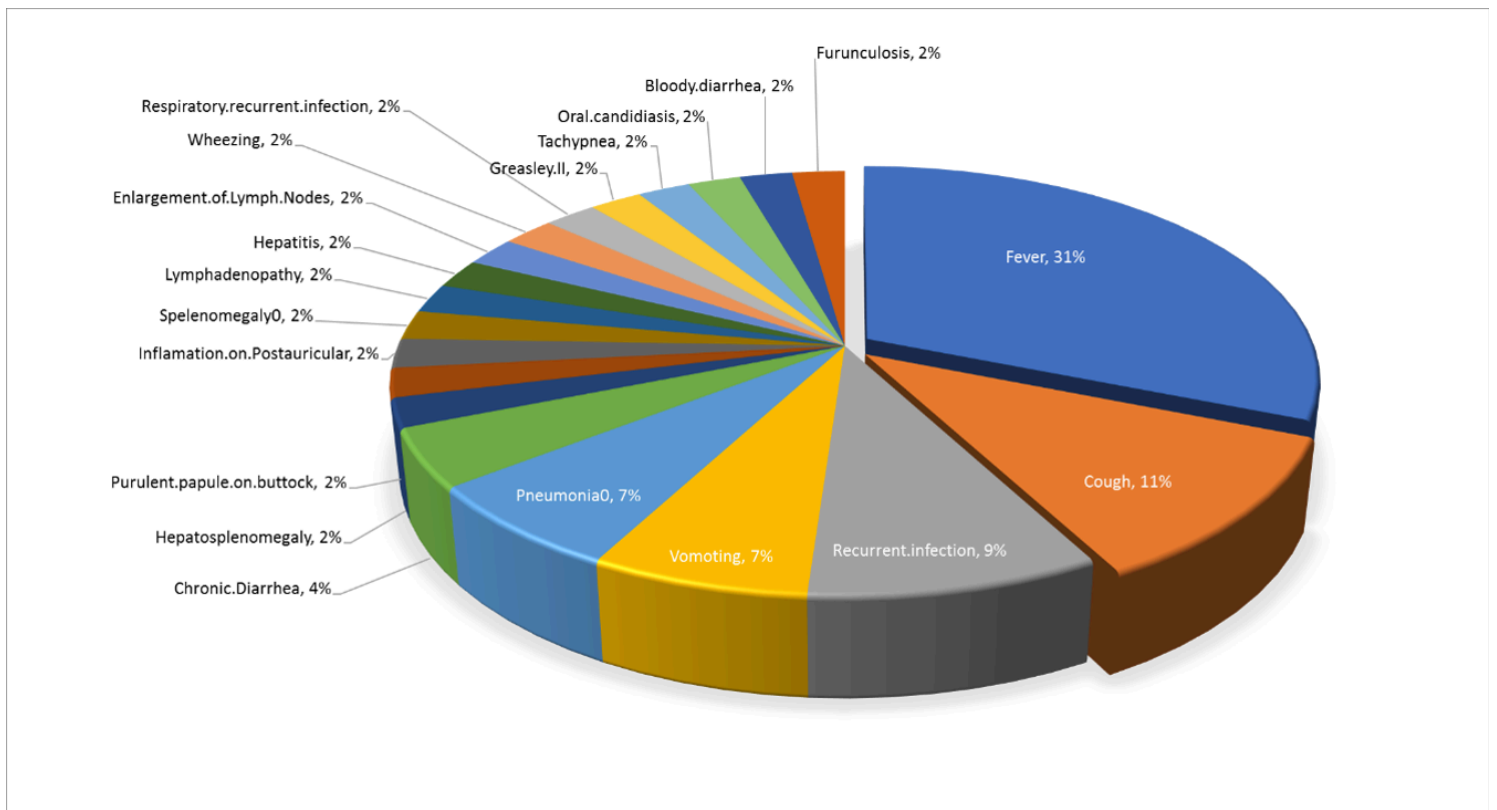


Figure 2

Initial clinical presentations at disease onset in patients with CHS (n = 23). Only symptoms recorded prior to diagnosis were included. Each patient is counted once per symptom.