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Review Article

Lymphopenia in Children: A Review

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Abstract

Lymphopenia to the child is defined by a decrease in lymphocytes number under normal value correlated to age. It is a non-exceptional situation in pediatrics and research must be conducted methodically. In children, it must be identified according to the inversion of the leucocytes range, before 4 years of age. The investigation strategy should be guided by the context that identify the causes. In children, the usual viral diseases are the main cause of lymphopenia, less than 15 days, in healthy style conditions or severe COVID-19. In the context of unusual infection, we must think about HIV infection, and Severe Combine Immunodeficiencies (SCID), even if we have young child. Sometimes the context and very typical, such as malignant hemopathy or chemotherapy. When a child present autoimmunity symptom, a lupus must be evocated. A context of chronic diarrhea should orient to exudative enteropathy, even if we have edema and hypoalbuminemia. When the context is not evocative, then think about Waldmann's lymphangiectasia, zinc deficiency. A clinical context-oriented assessment often leads to the cause of lymphopenia. Our aim is to propose an etiological diagnosis strategy, based on the clinic and some complementary examinations.

Keywords: *Lymphopenia; HIV; COVID-19; Immunodeficiencies*

Introduction

In children, lymphopenia is defined by a decrease in the number of circulating lymphocytes below the norms for age [1]. Confirmation is made on two different samples and interpretation in absolute value. The discovery can be integrated into an evocative clinical context or be fortuitous. It is far from exceptional, particularly in serious childhood diseases where the evolution can be unfavorable [2]. It must first eliminate a severe combined deficiency of immunity which is a real diagnostic and therapeutic emergency. Our objective is to propose a diagnostic approach, in order to guide the etiological search, in the face of lymphopenia in children.

Normal values of lymphocytes and their subpopulations in children

Before the age of 2 years, lymphopenia is defined by a count below 3000 lymphocytes/mm3. In young children, there is physiological lymphocytosis until the age of 4 years. In infants under 3 months, the lymphocyte count is usually higher, and exceeds 2800/mm^3 [3]. The evolution of the number of lymphocytes according to age is presented in figure 1 [4]. In the presence of lymphopenia, the study of lymphocyte sub populations (SPL) makes it possible to determine the biological profile and guide etiological research. Table 1 illustrates the normal values of Lymphocyte sub populations (SPL), according to age.

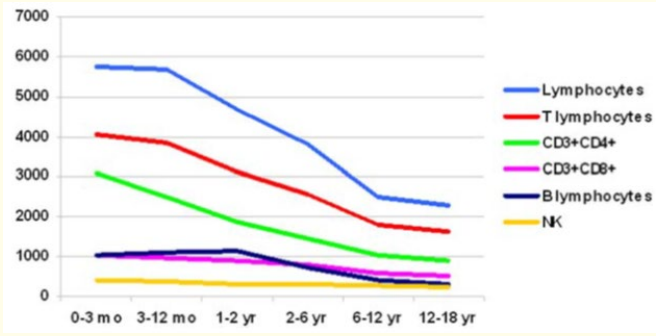

Figure 1: *Lymphocytosis according age [4].*

	AGE GROUPS					
SUBSETS	0–3 MONTHS	3–12 MONTHS	1–2 YEARS	2–6 YEARS	6–12 YEARS	12–18 YEARS
Lymphocytes	5740 (4054–7048)	5690 (3320–7006)	4685 (3873–6141)	3800 (2340–5028)	2500 (1662–3448)	2285 (1340–3173)
CD3+	4040 (3180–5401)	3833 (2284–4776)	3133 (2542–4933)	2580 (1578–3707)	1793 (1239–2611)	1629 (954–2332)
CD4+	3079 (2330–3617)	2492 (1523–3472)	1866 (1573–2949)	1448 (870–2144)	1030 (646–1515)	887 (610–1446)
CD8+	1048 (712–1361)	976 (524–1583)	884 (656–1432)	804 (472–1107)	595 (365–945)	518 (282–749)
CD16/56+	408 (201–870)	381 (230–801)	296 (186–724)	299 (155–565)	262 (120–483)	230 (87–504)
CD19+	1032 (315–1383)	1123 (776–2238)	1152 (733–1338)	730 (434–1274)	403 (276–640)	321 (173–685)

Table 1: *Normal values of lymphocytes sub populations (SPLs), as a function of age, mean (10th and 90th percentile) in 106/l [4].*

Pathogenesis of lymphopenia in children

Lymphopenia is the biological translation of a constitutional or acquired abnormality. It can be benign and transient or associated with serious conditions [3]. It can be global or selective, affecting a particular lymphocyte sub population [5]. In children, chronic lymphopenia below 500/mm^3 exposes them to the risk of opportunistic infections, which can be life-threatening [3]. It is typically the result of four major mechanisms [1]:

1. Production deficiencies, related to a primary immune deficiency or secondary to malnutrition and/or zinc deficiency;
2. Excess catabolism, due to HIV infection, systemic lupus erythematosus or some treatments such as chemotherapy, radiotherapy and immunosuppressive treatments;
3. Changes in lymphocyte distribution, observed during some viral infections, granulomatous diseases and some situations such as hypersplenism, extensive burns, septic shock and corticosteroid therapy;
4. Poorly understood mechanisms: lymphomas, solid tumors, renal failure, idiopathic CD4 lymphopenia.

Etiology research of lymphopenia

In the face of lymphopenia, the etiological approach is based on questioning, a physical examination and additional examinations. Questioning allows us to look for a notion of consanguinity, diseases known as primary immunodeficiency, similar cases in the family. It is also necessary to look for a history of autoimmunity, chronic inflammation, recurrent and/or severe infections, opportunistic germs, such as diarrhea, thrush, interstitial pneumopathy and specify the current treatments (chemotherapy, corticosteroid therapy, immunosuppression).

Physical examination allows us to assess the general condition, hemodynamic state, consciousness. It allows us to look for growth retardation, visceral, pulmonary, digestive, cutaneous, neurological involvement, adenopathies, hepatosplenomegaly, edema, an infectious context, autoimmunity. The blood count must be repeated and all other lines must be analyzed, looking for other associated cytopenias, infectious or inflammatory signs. The lymphocyte sub population count makes it possible to specify the global or selective nature of the lymphopenia. It is requested as a second-line test, with serum protein electrophoresis and immunoglobulin weight determination. Viral serologies (HIV, CMV, Erythrovirus, or Parvovirus B19, COVID-19, etc.), vaccine serologies, plasma zinc level determination, autoimmunity testing (anti-nuclear Ab, anti-native DNA Ab), cyto-puncture and lymph node biopsy are requested as a third-line test, depending on the context. HLA-DR expression and genetic study make it possible to confirm the etiologies and are carried out in specialized laboratories. In all cases, etiological research must take into account age, context, clinical and biological symptoms, as well as current treatments [5].

Main etiologies When faced with lymphopenia in children, it is necessary to distinguish suggestive contexts from less suggestive contexts. When faced with a suggestive context, the causes are dominated by immune deficiencies, lupus and zinc deficiency. The younger the child, the more likely the hypothesis of Immune Deficiency (ID) is, particularly in the context of opportunistic infection (Pneumocystis, CMV, candida, etc.). HIV infection should be systematically sought, especially if there is hepatosplenomegaly, adenopathies and risk factors. During the COVID-19 pandemic, studies have shown the importance of hematological abnormalities in predicting the severity of the disease [6]. Indeed, a high prevalence of lymphopenia has been observed in severe forms of the disease, suggesting a relationship between lymphopenia and severity of COVID, despite the small size of pediatric series [6]. However, the existence of comorbidity has always been a significant risk factor [6]. The average lymphocyte count in children with COVID 19 was (39.1 ± 21.4%) [6]. The norm for lymphocyte count in children under 2 years of age was 3.5-11 x10^9/L, between 2 and 6 years of age it was 6-9 x10^9/L and beyond 6 years of age: 1-5 x 10^9/L [6]. In classic viral infections, lymphopenia is usual but transient, in a child generally in good general condition. It is particularly seen in Cytomegalovirus (CMV) infections, in varicella and zoster (VZV) and in Erythrovirus (Parvovirus B19) infection. Once these infections are ruled out, Severe Combined Immune Deficiency (SCID) is considered, especially if there is consanguinity and/or similar cases in the family. The main SCIDs are illustrated in table 2.

<table>
<tr><td colspan="6">I. Immunodeficiencies affecting cellular and humoral immunity.
(a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia*.</td></tr>
<tr><td colspan="3">CD19 NL : SCID T- B+</td><td colspan="3">CD19 ↓ : SCID T-B-</td></tr>
<tr><td>SCID T-B+NK-</td><td colspan="2">SCID T-B+NK+</td><td>SCID T-B-NK-</td><td colspan="2">SCID T-B-NK+</td></tr>
<tr><td rowspan="3">XL,
CD 132 def
γc deficiency
IL2RG

AR,
CD 132+
JAK-3 def
JAK3</td><td>IL7Rα .
IL7R</td><td>Coronin-1A def *.
CORO1A
Detectable thymus</td><td rowspan="3">ADA def . ADA
Chondrosternal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects

Reticular dysgenesis. AK2
Neutropenia, deafness. Some have anemia and thrombocytopenia.

Activated Rac2 defect*.
RAC2, AD GOF
Recurrent bacterial and viral infections, lymphoproliferation; neutropenia</td><td colspan="2">Microcephaly ?</td></tr>
<tr><td>No γ/δ T cells:
CD3δ*. CD3D
CD3ε*. CD3E
CD3ζ** . CD3Z

Nl γ/δ T cells :
CD45*
PTPRC</td><td>Winged helix def*.
FOXN1.

Severe infections; abnormal thymic epithelium; congenital alopecia, nail dystrophy, neural tube defect. Ig: decreased .Tc: Very low.</td><td>Yes
Radiation sensitivity
- With facial dysmorphism:
DNA ligase IV def .
LIG4

CERNUNNOS /XLF def*. NHEJ1.

- Without facial dysmorphism:
DNA PKcs def*PRKDC
Variable Ig levels</td><td>No
Increased risk of graft rejection, possibly due to activated NK cells

RAG 1/2 def
(RAG1/ RAG2)

DCLRE1C def
DCLRE1C
(ARTEMIS).
+ Radiation sensitivity</td></tr>
<tr><td>LAT def* . LAT.
Typical SCID or CID with adenopathy, splenomegaly, autoimmunity. High Ig.</td></tr>
</table>

Table 2: *Main severe combined immunodeficiencies (SCID) [23].*

Indeed, the incidence of primary immune deficiencies is underestimated in the world. In Morocco, it would be 3324 new cases per year in 2011, according to Bousfiha., *et al* [7].

Di-George syndrome is a congenital primary DI due to a microdeletion on the long arm of chromosome 22 (in 22q1). It often associates cardiac malformations, recurrent infections, persistent hypocalcemia by hyperparathyroidism and lymphopenia. In California, out of 993,000 newborns screened for SCID, 50 had T-cell lymphopenia (0.005%) including one case of Di-George syndrome [8]. Ataxia-Telangiectasia manifests as cerebellar ataxia around the age of walking, ocular telangiectasias, recurrent respiratory infections and T-cell lymphopenia, with risk of lymphoid hemopathies [9].

The genetic anomaly is a mutation of the ATM gene [10]. Zinc deficiency is also a cause of lymphopenia. In a Brazilian series, in children hospitalized for malnutrition, correction of lymphopenia was correlated with an increase in zinc levels [11].

Systemic lupus erythematosus (SLE) is also a cause of lymphopenia, particularly in older children. This systemic autoimmune disease is diagnosed in 10 to 17% of cases before the age of 16. However, initial presentations with pediatric onset are more severe [12]. Diagnosis is based on the American College of Rheumatology SLE classification criteria [11]: Malar erythema, discoid lupus, photosensitivity, oral or nasopharyngeal ulcers, arthritis, pleurisy and/or pericarditis, proteinuria greater than 0.5g/24h or red blood cell casts, psychosis or convulsion, hemolytic anemia or leukopenia (less than 4 G/L) or lymphopenia (less than 1.5 G/L) or thrombocytopenia (less than 100 G/L), antinuclear antibodies, anti-native DNA antibodies or anti-Sm antibodies or anti-phospholipid antibodies. Diagnosis is made if at least 4 of the 11 criteria are present. In a multicenter study, lymphopenia was significantly associated with systemic lupus erythematosus in Brazilian children and adolescents [13].

There are several other etiologies whose context is suggestive such as hypersplenism, renal failure, extensive burns, shock. Indeed, it has been found that critically ill and lymphopenic 3-month-old infants were significantly more likely to require active resuscitation and intensive care, regardless of the total leukocyte count [14]. Furthermore, in severe sepsis in children, early and persistent lymphopenia is a risk factor for mortality, due to multiple organ failure [15]. In lymphomas, the mechanism remains poorly understood. However, in Hodgkin's lymphoma, lymphopenia is frequently correlated with the stage of the disease. Indeed, Sternberg cells and those of the inflammatory infiltrate secrete many soluble factors involved in local cell recruitment, control of lymphocyte activation and differentiation, and apoptosis. Thus, B lymphopenia occurs earlier than T lymphopenia, which occurs at more advanced stages of the disease [16]. Post-therapeutic lymphopenia is also described in immunosuppressive treatments: prolonged corticosteroid therapy, radiotherapy, chemotherapy. In the Tunisian series of Ben Nasr., *et al*. patients who had lymphopenia during Hodgkin's lymphoma more frequently presented with febrile neutropenia during chemotherapy [17]. In less suggestive contexts, it may be a question of exudative enteropathies or idiopathic CD4 T lymphopenia. In Waldmann's disease or primary intestinal lymphangiectasia, there is a congenital malformation of the lymphatic drainage of the gastrointestinal tract, characterized by dilated lymphatic vessels and enlarged villi causing lymph to leak into the intestinal lumen [18]. The loss of lymph leads to hypoproteinemia with hypoalbuminemia, hyogammaglobulinemia and lymphopenia [19-21]. As for idiopathic CD4+ T lymphopenia, it is rarer in children than in adults [5]. In all cases, it remains a diagnosis of exclusion, with CD4+ lymphopenia ≤ 300/mm3 or ≤ 20% of total lymphocytes, persistent on two different samples, in the absence of an identified cause of lymphopenia, in particular HIV infection or a defect in the expression of HLA class II molecules [5,22]. It can be asymptomatic or revealed by opportunistic infections, the most common of which are Cryptococcal meningoencephalitis, autoimmune or neoplastic manifestations [22]. Management is similar to that of HIV infection. However, the use of specific immunotherapy can be discussed [5].

We propose a diagnostic approach for lymphopenia in children in table 3.

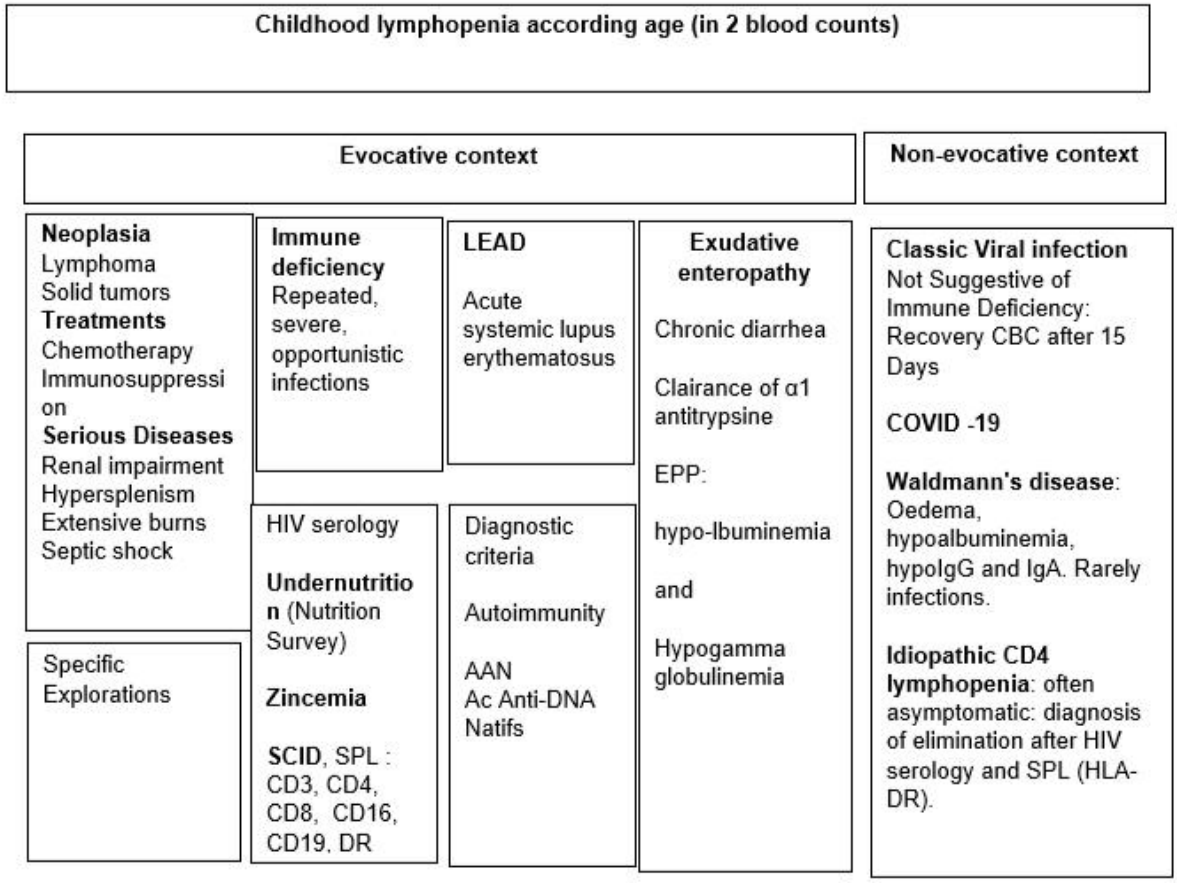

Table 3: *Diagnostic approach in children lymphopenia.*

Conclusion

Lymphopenia is a biological sign that can be benign, transient or associated with serious pathologies. It requires a complete evaluation, with an etiological aim. In children, lymphopenia is an essential element in the diagnosis of DICS, especially in infants and it should suggest Lupus in older children. Zinc deficiency should also be considered. In the absence of a suggestive context, Waldmann's disease should be considered.

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