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Hematological findings in lysosomal storage disorders: a perspective from the medical laboratory

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ABSTRACT

Lysosomal storage disorders (LSDs) are a group of rare and genetic diseases produced by mutations in genes coding for proteins involved in lysosome functioning. Protein defect leads to the lysosomal accumulation of undegraded macromolecules including glycoproteins, glycosaminoglycans, lipids, and glycogen. Depending on the stored substrate, several pathogenic cascades may be activated leading to multisystemic and progressive disorders affecting the brain, eye, ear, lungs, heart, liver, spleen, kidney, skin, or bone. In addition, for some of these disorders, hematological findings have been also reported. In this paper, we review the major hematological alterations in LSDs based on 56 case reports published between 2010 and 2020. Hematological alterations were reported in sphingolipidosis, mucopolysaccharidoses, mucolipidoses, neuronal ceroid

lipofuscinosis, glycogenosis, glycoproteinosis, cystinosis, and cholesteryl ester storage disease. They were reported alterations in red cell linage and leukocytes, such as anemia and morphology changes in eosinophils, neutrophils, monocytes, and lymphocytes. In addition, changes in platelet counts (thrombocytopenia) and leukocyte abnormalities on non-peripheral blood samples were also reported for some LSDs. Although in most of the cases these hematological alterations are not pathognomonic of a specific disease or group of LSDs, since they can be easily identified in general clinical laboratories, their identification may contribute to the diagnosis of these disorders. In this sense, we hope that this review contributes to the awareness of the importance of hematological alterations in the diagnosis of LSDs.

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1. INTRODUCTION

Lysosomal storage disorders (LSDs) are a group of monogenic metabolic diseases produced by mutations in genes encoding for proteins involved in the lysosomal function. These mutations lead to the synthesis of proteins with none or reduced activity, producing the progressive accumulation of partially degraded substrates into the lysosome [1]. Although the clinical, diagnostics, and pathophysiology can be heterogeneous, the

Table 1 Classification of lysosomal storage disorders

Group of LSD (Accumulated substrate)	Disease	Inheritance	OMIM number
Glycogenoses (Glycogen)	Danon Disease	X-LD	300257
	Pompe Disease	AR	232300
Glycoproteinoses (Glycoproteins)	Aspartylglucosaminuria Disease	AR	208400
	Fucosidosis	AR	230000
	Galactosialidosis	AR	256540
	α-Mannosidosis	AR	248500
	β-Mannosidosis	AR	248510
	Schindler Disease	AR	609241
	Sialidosis	AR	256550
Mucolipidoses (Mucolipids)	Type I-IV	AR	252500
Mucopolysaccharidoses (Glycosaminoglycans)	Type I (Hurler Syndrome)	AR	607014

	Type II (Hunter Syndrome)	X-LR	309900
	Type III (Sanfilippo Syndrome)	AR	252920
	Type IV (Morquio Syndrome)	AR	253000
	Type VI (Maroteaux -Lamy Syndrome)	AD	184095
	Type VII (Sly Syndrome)	AR	253220
	Type IX (Natowicz Syndrome)	AR	601492
	*MPS-Plus syndrome	AR	617303
Neuronal ceroid lipofuscinoses (Lipofuscin)	Type I – VIII	AR	256730
Sphingolipidoses (Sphingolipids)	Fabry Disease	X-L	301500
	Farber Disease	AR	228000
	Gaucher Disease	AR	231000
	GM1 Gangliosidoses	AR	230500
	GM2 Gangliosidoses	AR	272800
	Metachromatic leukodystrophy	AR	250100
	Niemann-Pick A, B, C	AR	257200
	Krabbe Disease	AR	245200
Unclassified LSD	Cystinosis	AR	219750
	Cholesteryl ester storage disease	AR	278000
	Free sialic acid deposition disorders	AR	269920
	Multiple sulphatase deficiency	AR	272200
	Pycnodysostosis	AR	265800

*AR: Autosomal recessive. X-LD: X-linked dominant. X-LR: X-linked recessive. *Recently described in Turkish and Yakut (Russian) patients (See [13]). Note that MPS V (Sheie syndrome) is not included in the table since it was later recognized as an attenuated form of MPS I. Similarly, MPS VIII is not included since after being proposed, it was recognized as a laboratory pitfall and the proposal was withdrawn [14].*

LSDs can be classified into 7 groups according to the accumulated general substrate (Table 1).

The diagnosis of a LSDs is based on clinical evaluation of the patient and laboratory tests such as the evaluation of the enzymatic activity [2], or the primary stored substrate (e.g., glycosaminoglycans, oligosaccharides, sphingolipids, and glycogen, among others) [3, 4]. Molecular diagnosis is still difficult considering the lack of complete understanding of the clinical implications of novel variants [5-7]. Nevertheless, molecular diagnosis should be considered during the diagnosis of some LSDs, such as neuronal ceroid lipofuscinosis [8]. Moreover, lyso-Gb3 for Fabry disease (FD) or macrophage inflammatory protein 1-alpha (MIP-1α) in Gaucher disease (GD) have been suggested as novel biomarkers of these LSDs [5]. Chitotriosidase has also been proposed as a biomarker for some LSDs such as GD [9], cystinosis [10], GM1 gangliosidoses [11], and Niemann-Pick type C [12]. Particularly in GD, some hematological alterations on macrophages are frequently found in both smear blood and biologic fluids (i.e., Bronchoalveolar lavage-BAL), which may contribute to the diagnosis. Nevertheless, leukocyte abnormalities also can be found in other LSDs. In this review, we described the major hematological alterations in LSDs found in 56 case reports published between 2010 and 2020. Reference values of all hematological findings were adjusted to the guidelines on standard operating procedures for hematology of the World Health Organization (WHO).

2. LSD AND GENERAL DIAGNOSIS

Lysosomes were first described in the 1950s by Christian De Duve, who recognized the role of this organelle in the degradation and recycling of intracellular and extracellular macromolecules [15]. During the last decade, they have been recognized other lysosomal functions due to the fundamental role as a metabolic hub, influencing and sensing diverse nutrient processes, secretion, gene regulation, plasmatic membrane repair, ionic homeostasis, immune response, and cholesterol transport, among others [16]. The lysosomal biogenesis is triggered by the transcription factor EB (TFEB), which is a master regulator of the lysosomal biogenesis and influences the interaction of the lysosome with other organelles and the cellular homeostasis [16].

LSDs are a group of about 70 monogenic metabolic disorders caused by the deficiency of a specific protein (i.e., enzyme, transporter, or cofactor) involved in the lysosomal function. This deficiency leads to the lysosomal accumulation of partially degraded substrates that generates and spectrum of clinical manifestations depending of the stored substrate and the affected tissues [17]. LSDs have an overall prevalence between 1 in 4,000 and 7,000 live births. Nevertheless, the exact prevalence of LSDs is difficult to calculate due to their wide heterogeneity, which sometimes leads to misdiagnosis [5]. An important group of LSDs are associated with central nervous system (CNS) impairment, while others are mainly characterized by their effect on peripheral organs. The reader is referred to recent review for more details about LSDs [18].

3. DIAGNOSIS

Given the enormous heterogeneity found in the LSDs, the diagnosis is always a challenge, and it requires a common effort between clinicians, biochemists, and medical laboratory scientists to achieve an adequate and timely diagnosis. In this sense, clinical suspicion should be accompanied by accurate routine and specialized laboratories.

3.1 Clinical approach

LSDs clinical manifestation mainly depends on the stored substrate and the affected tissues.

Usually, the storage substrate occurs in the organs where the substrate is synthesized (i.e., liver, spleen, bone, brain, muscle). In this sense, the accumulation of the substrate will generate a disruption of the cellular homeostasis, inducing cellular damage, mitochondrial stress, apoptosis, dysregulation of redox processes, and disruption of the lysosome in/out transport [19-21]. Phenotypic features of patients with LSDs vary depending of the stored substrate and may include coarse face, short stature, skeletal abnormalities, hepatosplenomegaly, cardiac and lung disease, eye and ear impairment, and central nervous system involvement [5, 18].

3.2 Laboratory approach

As previously noted, the diagnostic confirmation of a LSD requires a specialized laboratory including the identification of biomarkers (e.g., stored substrate quantitation), determination of enzymatic activities, and molecular diagnosis. In these scenarios, important advances have been reached. For instance, the measure of GAGs by several qualitative and quantitative methods such as alcian blue, toluidine blue, paper, and thin-layer chromatography, high-pressure chromatography, gas chromatography, mass spectrometry is used in MPS diagnosis and follow up [22]. Collagen type II, β-galactosidase, nidogen-1, and fatty acid-binding protein are also used in MPS [23]. For FD, it has been proposed the globotriaosylsphingosine determination, whereas the measure of chitotriosidase is used for GD. Other biomarkers for GD include glucosylsphingosine, macrophages protein 1-alpha and 1-beta, cathepsin K and osteopontin [23]. For sphingolipidoses such as Krabbe, the psychosine has been described as a biomarker, which may determine the progression of the disease [23], whereas the cholestane-3β, 5α, 6β-triol (C-triol), and 7-ketoholesterol seem to be a sensible biomarker in Niemann-Pick type C (NPC) [24, 25]. In glycogenoses, as in Pompe disease, the most known biomarker is tetrasaccharide glucose (Glc4), which correlates with therapy response. Other two biomarkers, myostatin and insulin-growth factor I (IGF-I), can also be used in Pompe disease [23, 26]. These biomarkers could be useful in pseudo-deficiencies, as reported for MPS I, MPS VII, and GD [27, 28], for which the traditional biochemical tests not always lead to a specific diagnosis. The enzyme activity determination is the gold standard for the diagnosis of LSDs produced by the impairment of an enzyme. This activity can be assayed in a wide range of biological samples such as plasma, serum, leukocytes, cultured fibroblasts, chorionic villi, amniotic fluid, cultured amniocytes, and dried blood spots [29]. Finally, the molecular diagnosis can helpful to establish the diagnosis and genetic counseling interventions [3], and is the gold standard for other conditions as neuronal ceroid lipofuscinosis [8]. Nevertheless, biomarker-, enzyme activity-, or molecular-based diagnosis of LSDs requires highly specialized facilities and trained personnel. In contrast, the analysis of the hematological abnormalities, which can help in the diagnosis of some LSDs, can be performed in low and high-complexity laboratories. In this sense, in the next sections, we will review the complexity of the hematopoietic system and the major alterations reported in some LSDs.

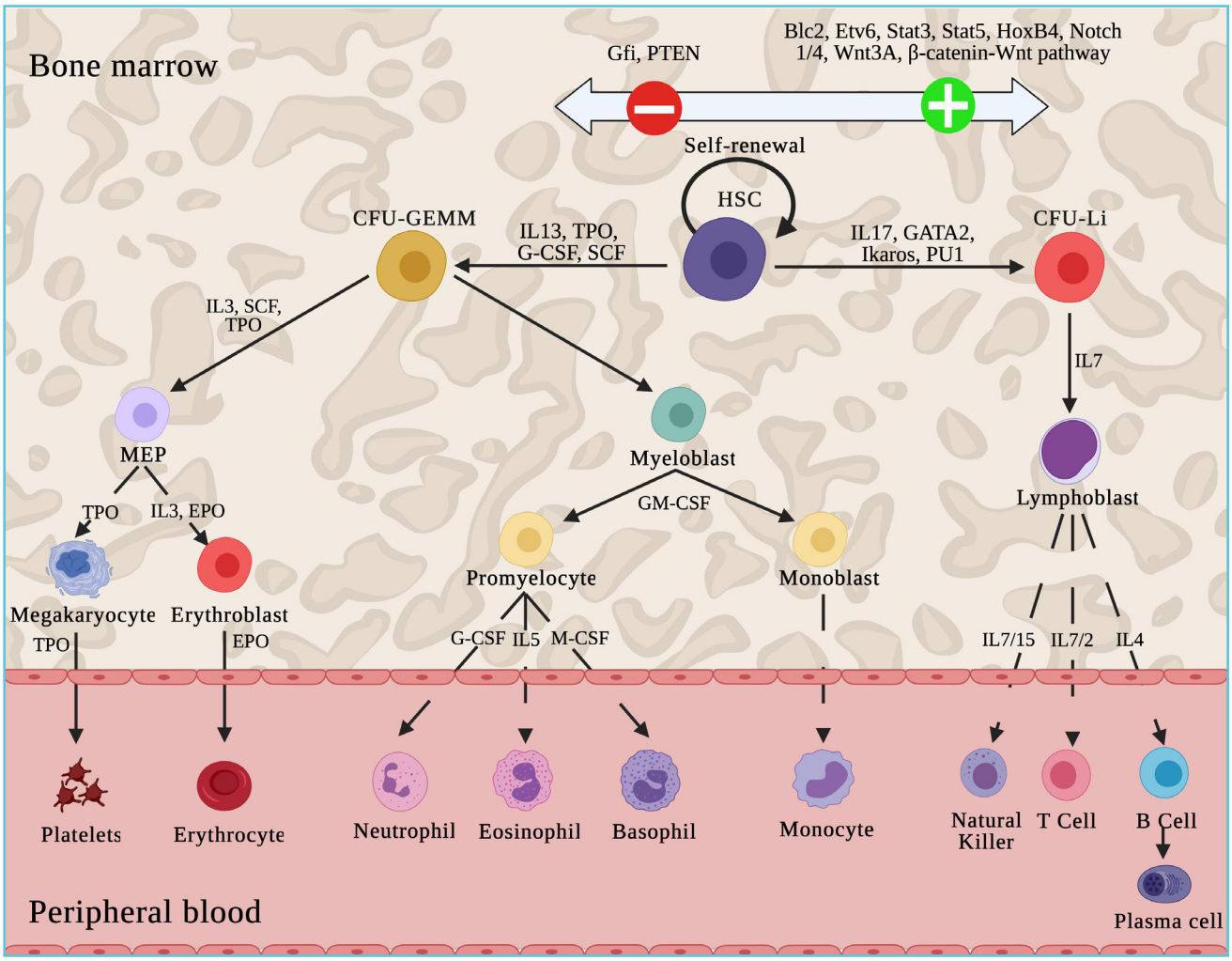
4. OVERVIEW OF THE HEMATOPOIETIC SYSTEM

Hematopoietic stem cells (HSC) are considered the foundation of the adult hematopoietic system and have a crucial role in the long-term maintenance and production of all mature blood cell lineages. Pioneering studies by Till and McCulloch, 1960 and Becker *et al.*, 1963; using transplantation experiments demonstrated the clonality of the adult hematopoietic system

and indicated that the majority of blood cells originate from very few/unique multipotent HSCs capable of proliferation, differentiation, and self-renewal [30]. These HSC-independent hematopoietic cells originate in the embryo and persist in the adult hematopoietic system [31, 32]. Whereas thrombopoietin, erythropoietin, colony-stimulating factor, and some interleukins promote the HSCs proliferation; several cytokines promote the HSC differentiation into multipotential colony-forming progenitor units (CFU) including: CFU-GEMM (Granulocytes, Erythrocytes, Monocytes, Megakaryocytes) for the myeloid lineage and CFU-Li (T, B or NK cells) for the lymphoid lineage (Figure 1) [33, 34].

Since mature blood cells derived from HSC contain all the eukaryotic organelles, including lysosome, substrate accumulation observed in LSDs

Figure 1 **Hematopoietic landscape. HSCs are cells with unique characteristics of self-renewal, pluripotency, and differentiation**



Several pathways have been described like positive (+) and negative (-) modulators of self-renewal [35, 36]. Upon intrinsic and extrinsic signals (cytokines, growth factors, and transcription factors), HSCs can give origin to GFU-GEMM and CFU-Li to myeloid and lymphoid precursors, respectively [37]. In contrast with the BM, where the blood cells precursors are present, in the bloodstream only mature cells are found which are virtually distributed around the body. All the blood cells, except the erythrocyte and platelets, maintain their organelles including the lysosomes. This figure was created using BioRender.com.

can affect not only the hematopoietic precursors but also the most differentiated cells as red blood cells, leukocytes, and thrombocytes or even platelets [38, 39]. In Table 2, we summarize the normal values for the blood count and in the next sections, we describe the normal findings of the blood cells as well as their alteration in the LDS context.

Table 2 Reference values of hemogram

Lineage	Parameter	Units	0-2 years	2-5 years	Men	Women
Red cell lineage	Red blood cells	Cells/µL	4.5±0.8	4.6±0.7	$5x10^6$	$4.5x10^6$
	Hemoglobin	g/L	120 ± 15	125 ± 10	140 - 175	123 - 153
	Hematocrit	%	36 ± 3	37 ± 3	42 - 50	36 - 45
	MCV	fL	78±8	81±6	87±7	
	MHC	pg	27±4	27±3	29±2	
	RDW	%	13.6 ± 2	12.8 ± 1.2	13 ± 1.5	
	Reticulocytes	%	1.0 ± 0.8		<2	
Leukocytes	Leukocyte count	Cells/µL	$6x10^3$ - $7x10^3$	$5.5x10^3$ – $15.5x10^3$	$4x10^3$ - $11x10^3$	
	Lymphocytes	Cells/µL	$3x10^3$ – $9.5x10^3$	$2x10^3$ – $8x10^3$	$1x10^3$ - $4x10^3$	
		%	44 – 74	35 – 65	20 – 40	
	Monocytes	Cells/µL	$0.5x10^3$		$0,15x10^3$ - $0,9x10^3$	
		%	5		2-8	
	Neutrophils	Cells/µL	$1,5x10^3$ - $8,5x10^3$		$2,5x10^3$ - $8,0x10^3$	
		%	15 - 45	25 - 57	55 - 65	
	Eosinophils	Cells/µL	$0,3x10^3$		$0,05x10^3$ - $0,5x10^3$	
		%	3		1 - 3	
	Basophils	Cells/µL	$0,1x10^3$		$0,025x10^3$ - $0,1x10^3$	
		%	0 - 1			
Platelets	Platelets	Cells/µL	$200x10^3$ - $400x10^3$		$150x10^3$ - $450x10^3$	

Values have been adjusted from WHO guidelines [40].

5. HEMATOLOGICAL ABNORMALITIES IN LSDS

We found a total of 51 articles that included 56 LSDs cases in which hematological parameters were evaluated. The reported cases included 26 sphingolipidosis, 13 MPS, 3 ML, 3 neuronal ceroid lipofuscinosis (NCL), 2 glycogenosis, 2 glycoproteinosis, 1 cystinosis, 1 cholesteryl ester storage disease (CESD), and 1 unclassified LSDs. Male patients were more frequently reported than females (57.2% male vs 42.8% female). The age for male patients was between 2 weeks and 68 years; whereas females ranged from newborn to 69 years. We focused on the hematological parameters before the establishment of any clinical intervention to identify baseline values and morphological changes in blood cells that could be associated with the disease. All data is summarized in Table 3.

5.1 Red cell lineage

Anemia was reported in 30.3% of the cases (17/56), with GD having the highest number of reports (64.7%), followed by cystinosis, CESD, NPC, ML IV, MPS I, and aspartylglucosaminuria, with 5.9% each one. Based on the MCV, 3 cases of microcytic anemia (MCV <80fL) were identified, all of them corresponding to GD. Although mild anemia was the main finding, one case reported a severe microcytic hypochromic anemia (Hb: 50 g/L; MCV: 66 fL, MCH: 19.4 pg) in a 1-year-old man diagnosed with GD type 1 with slight anisocytosis and poikilocytosis [41]. Interestingly, a 69 years-old Japanese female with GD type 1 and gastric cancer had a reduction in the erythrocytes count ($3.98x10^6$/µL) and hematocrit levels (34,6%), with marked reticulocytosis (20%) [42]. In this patient, a novel mutation c.587A>G (p.K157R) in the *GBA* gene was reported; however, the impact of this mutation on the β-glucocerebrosidase was not evaluated.

5.2 Leukocytes

As previously described, LSDs are a group of metabolic disorders characterized by substrate accumulation into the lysosome [1]. In this sense, it could be expected that the major hematological findings are related to the leukocyte morphology due to the presence of organelles in these cells [43]. The reader is referred to some of the reviewed publications for representative images of leukocytes alterations [44-48].

5.2.1 Granulocytes

Basophil abnormalities were not reported on any of the revised cases. On the other hand, eosinophils with enlarged and sparse granules in the blood smear were reported in three cases of GM1 gangliosidoses [44, 49, 50]. Although these alterations have been recognized since early reports as frequent alterations of GM1 gangliosidoses [51], they are not routinely investigated as part of suspicion of GM1 gangliosidoses unless the absolute leukocyte count is altered. Eosinophils with deep pink-blue granules were reported in a MPS type VI female patient, as well as abnormal lobulation on neutrophils [52]. These findings were observed after an alteration in the automated analysis, which led to a suspicion that was later confirmed as pseudobasophilia. On the other hand, the Alder-Reilly anomaly was identified on neutrophils from MPS I, IV, and VI patients [45, 52-55], representing a potential finding for this LSD group. Although we did not find the Alder-Reilly anomaly in the reports for other LSDs, it is not possible to discard its presence in entities different than MPS. In addition, Alder-Reilly inclusions must not be confused with toxic granulations that are restricted to neutrophils in a transitory form during an inflammatory process [43].

5.2.2 Monocytes

Despite the crucial role of monocytic cells, morphology alterations were not frequently

reported in the peripheral blood of LSDs patients. However, some dense blue/purple-black granules have been occasionally reported in monocytes from MPS patients [54, 55], which are metachromatic after toluidine staining [46]. Nevertheless, the most common findings on monocytes seem to be restricted to the phagocytic activity of the macrophages from BM, liver, and spleen. These changes will be discussed later.

5.2.3 Lymphocytes

Morphologic alterations in lymphocytes were reported in almost all the LSDs cases reviewed. Vacuolated lymphocytes were reported in GM1 gangliosidoses [49, 56], ML [57], and MPS III [58]. This vacuolization was accompanied by Alder-Reilly inclusions in MPS IIIA [47], MPS IIIB [59], MPS IV [54] and MPS VII [59]. In ML type II (I-cell disease) vacuole-like inclusions are frequently observed on lymphocytes, in which accumulation of HLA class II molecules have been observed, suggesting a role of N-acetylglucosamine-1-phosphotransferase in the immune system [60]. In this sense, the study of the chemical nature of the inclusions may increase our knowledge about the physiopathology of the disease and lead to the identification of novel therapeutic targets. On the other hand, atypical and reactive states of lymphocytes were reported in one case of GD [61] and aspartylglucosaminuria [62], respectively. Also, electronic microscopy of peripheral blood samples allowed the identification of cytoplasmatic vacuoles containing electrodense periodic structures in lymphocytes from NCL patients [63-65].

In Pompe disease, it has been reported that vacuolation of lymphocytes [66] is a consequence of the lysosomal glycogen accumulation [67]. Electronic microscopy of peripheral blood cells, allowed the identification of inclusions in samples from Pompe disease patients [68]. Despite vacuolization is being suggestive of lysosomal storage, the use of a specific glycogen staining (i.e., periodic acid-Schiff, PAS), allows a more accurate diagnostic impression. This was validated by Hagemans *et al*., through the analysis of PAS-stained blood films obtained from 65 patients with classical infantile and adult forms of Pompe disease, with a sensitivity and specificity of 100% and 98%, respectively [69].

5.3 Platelets

We found platelet counts in 25 out of the 56 case reports reviewed. In 60% of the cases (15/25), it was reported a marked thrombocytopenia (< 95 $x10^3$cells/µL), without abnormalities in the morphology. Although most of the reports are from GD patients (7/15) [48, 70, 71], it was also reported in Niemann-Pick type B [72] and C [73]; MPS II [74], MPS VII [75], aspartylglucosaminuria [62], and cystinosis [76]. One case of thrombocytosis (595 $x10^3$cells/µL) was reported in a 5 months-old female Pompe disease patient [66], whereas in one case the use of electronic microscopy allowed the visualization of granular inclusions on platelets from a 59 years-old Pompe disease patient [68].

5.4 Leukocyte abnormalities on non-peripheral blood cells

The major goal of this review article was to describe the more common hematological findings in LSDs with a particular focus on the blood smear due to its routine use in medical laboratories. Nevertheless, interesting changes of leukocytes, particularly in monocyte-derived lineage, have been registered in several biological samples which are summarized in Table 4. For instance, for GD it has been described the presence of Gaucher cells in BM [80, 86]. Gaucher cells are very large cells, usually macrophages, with a diameter between 20 and 80 µm with a small and eccentrically placed nucleus as well as a cytoplasm with wrinkles or striations [87].

Table 3 Summary of hematological abnormalities in LSDs patients

LSD	Red cell lineage	White line				Platelets	Ref.
		Eosino-phils	Neutro-phils	Mono-cytes	Lympho-cytes		
Gaucher	Anemia				Atypical	Thrombocytopenia	[41, 48, 61, 70, 71, 77-80]
Niemann-Pick	Anemia					Thrombocytopenia	[72, 73, 81, 82]
GM1 Gangliosidoses		Enlarged and sparse granules			Vacuolated		[44, 49, 50, 56]
Pompe					PAS-positive vacuoles	Thrombocytosis	[66, 68, 69]
Cystinosis	Anemia					Thrombocytopenia	[76]
CESD	Anemia						[83]
MPS I			AR				[45]
MPS II			AR			Thrombocytopenia	[53, 74]
MPS III A-B					Vacuoles with AR		[47, 58, 59]
MPS IV			AR	Blue/ purple-black granules	AR		[54]
MPS VI		Deep pink-blue granules	Abnormal lobulation and AR	Red-violet granules			[46, 52, 55]
MPS VII					Vacuoles with AR	Thrombocytopenia	[75, 84]
ML II					Vacuolated		[57, 60]
ML IV	Anemia						[85]
Asp.	Anemia				Reactive	Thrombocytopenia	[62]

MPS: Mucopolysaccharidosis. ML: Mucolipidosis. CESD: Cholesteryl ester storage disease. AR: Alder-Reilly anomaly. Asp: Aspartylglucosaminuria.

Table 4 Leukocyte abnormalities in non-peripheral blood samples from LSD patients

Sample	Technique	Leukocyte lineage	Findings	LSD	Reference
BM	GS	Myeloid	Histiocytes containing refractile crystal in the cytoplasm	Cystinosis	[76]
	HES	Myeloid	*Gaucher cells	Gaucher disease	[41, 48, 77, 79, 86, 92, 93]
	EM	Myeloid	*Gaucher cells	Gaucher disease	[80]
	APS	Myeloid	Histiocytes strongly positive	Gaucher disease	[42]
	GS	Myeloid	Foamy macrophages	Niemann Pick disease	[81, 88]
	TBS	Myeloid	Macrophages with metachromatic granules	MPS III	[58]
	WRS/GS	Lymphoid	**Azurophilic inclusions type dots or commas in plasma cells	MPS IIIA	[47]
Spleen	HES	Myeloid	*Gaucher cells	Gaucher disease	[70]
BAL	PPS	Myeloid	Foamy macrophages	Niemann Pick disease	[89]
Liver biopsy	NA	Myeloid	Foamy macrophages	Niemann Pick disease	[90]
CSF	WRS/GS	Myeloid	Intracytoplasmic granules in macrophages with haloes	MPS I	[91]

*BM: Bone marrow. BAL: Bronchoalveolar lavage. CFS: Cerebrospinal fluid. MPS: Mucopolysaccharidosis. NA: Not available. GS: Giemsa staining. HES: hematoxylin and eosin staining. EM: Electron microscopy. APS: Acid phosphatase stain. TBS: Toluidine blue staining. WRS: Wright staining. PPS: Papanicolaou stain. *Despite these cells could be suggestive of Gaucher disease, the presence of pseudo-Gaucher cells in bone marrow can address an erroneous diagnosis impression when routine hematoxylin-eosin staining is performed. To identify true Gaucher cells, iron staining is recommended and typically the presence of diffuse iron staining should be observed in Gaucher cells which is absent on pseudo-Gaucher cells [94]. **These findings are compatible with MPS I, II, and III when are present on peripheral lymphocytes; however, if these inclusions are found in plasma cells on bone marrow the major clinical suspicion is MPS III.*

Likewise, in Niemann Pick disease type B and C foamy macrophages have been observed in BM, bronchoalveolar lavage, and liver biopsy [88-90]. Histiocytes with refractile crystal in BM [76], and macrophages with intracytoplasmic granules in cerebrospinal fluid [91], were found in cystinosis and MPS I, respectively. Finally, azurophilic inclusions in plasma cells were found in BM from MPS IIIA patients [47].

6. CONCLUSIONS AND PERSPECTIVES

In LSDs, the accumulation of undegraded macromolecules into the lysosome triggers complex pathogenetic cascades leading to the clinical manifestations of these diseases. Impaired metabolism of lysosomal substrates may affect the autophagic-lysosomal system, the ubiquitin-proteosome system, the lysosome membrane permeability, and promotes inclusion body formation, dysregulation of the signaling pathway, inflammation, calcium homeostasis abnormalities, mitochondrial dysfunction, and oxidative stress [18].

These cellular changes may affect several tissues leading to different clinical manifestations, including hematological alterations. Although these hematological alterations may not be common findings in LSDs, they may contribute to the diagnosis of the disease, especially considering that the tests to evaluate these hematological abnormalities are available in most clinical laboratories. Nevertheless, health care professionals need to be aware of hematological alterations and correlate them with patient symptoms and other clinical laboratory results. In addition, it is necessary to extend the study of hematological alterations to other LSDs to explore the potential of these abnormalities as a biomarker for diagnosis or treatment follow-up.

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Author contributions

A.F.L., W.G.N., E.C., H.P., wrote the original draft. A.F.L., C.J.A.D., reviewed and edited the manuscript. All authors contributed to the literature analysis. All authors have read and approved the final manuscript.

Competing interests

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the review.

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