MJHID Educational Clinical Case

A nine-month-old-boy with Atypical Hemophagocytic Lymphohistiocytosis

Monia Ouederni1,2, Monia Ben Khaled1,2, Samia Rekaya1,2, Ilhem Ben Fraj1,2, Fethi Melloul1,2 and Mohamed Bejaoui1,2

1 Pediatric Immuno-hematology unit, bone marrow transplantation center Tunis
2 Faculty of Medicine, University of Tunis El Manar, Tunisia

Competing interests: The authors have declared that no competing interests exist.

Abstract. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammation caused by uncontrolled proliferation of activated lymphocytes and histiocytes. Often, HLH is an acquired syndrome. We report a case of a nine month-old-boy presented with hepatosplenomegaly, severe anemia, thrombocytopenia, hypertriglyceridemia and high hyperferritinemia. These clinical features of HLH prompted a wide range of infectious and auto-immune tests to be performed. After an extensive diagnostic workup, he was referred to the immune-hematologic unit for HLH suspicion with an unknown cause. Primary HLH due to familial lymphohistiocytosis (FLH) was first evoked in front of consanguinity, probable HLH in the family, early onset, and in the absence of a causative pathology like infection or cancer. However, functional tests were normal. Atypical features like the: absence of fever, hypotonia, recurrent diarrhea since diversification, hematuria, and proteinuria suggested an inborn metabolism error with gastrointestinal involvement. Specific tests were performed to reach a final diagnosis.

Keywords: Haemophagocytic lymphohistiocytosis, Inborn metabolism errors, Lysinuric protein intolerance, Familial lymphohistiocytosis, Hyperferritinemia, immunodeficiency.

Citation: Ouederni M., Ben Khaled M., Rekaya S., Ben Fraj I., Melloul F., Bejaoui M. A nine-month-old-boy with atypical hemophagocytic lymphohistiocytosis. Mediterr J Hematol Infect Dis 2017, 9(1): e2017057, DOI: http://dx.doi.org/10.4084/MJHID.2017.057

Published: October 16, 2017 Received: June 19, 2017 Accepted: October 4, 2017

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: Monia Ouederni, Centre National de Greffe de Moelle Osseuse de Tunis, Bab Saadoun, 2 Rue Jbel lakhdar, 1006 Tunis. Tel: 00 216 22 16 16 89, Fax: 00 216 71 56 53 68. E-mail: moniahasan@yahoo.fr

Introduction. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammation caused by uncontrolled proliferation of activated lymphocytes and histiocytes.1 The diagnosis of HLH is challenging in patients with prolonged fever, unresponsive to antibiotics. In 1994 the Histiocyte Society defined a set of diagnostic criteria; they were subsequently revised in 2004. The diagnosis of HLH can be established either by molecular diagnosis consistent with HLH and/or in presence of 5/8 clinical and laboratory criteria for HLH: fever, splenomegaly, cytopenia (affecting ≥2 of 3 lineages in peripheral blood), hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent NK cell activity, ferritin ≥500µg/l, soluble CD25 (soluble IL-2 receptor) ≥2,400 U/ml. Other supportive evidence includes cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH. All features of HLH can be explained by high concentrations of inflammatory cytokines and organ infiltration by activated lymphocytes and histiocytes.2,3
HLH can be primitive in children, underlying inherited immune deficiencies. Primary HLH is an autosomal recessive or X-linked primary immune deficiency including familial HLH (FLH) in which the clinical syndrome of HLH is the only manifestation. Four subtypes of FLH are defined by mutations in the following genes: PRF1 in FHL2, UNC13D in FHL3, STX11 in FHL4, and STXBP2 in FHL5. The Chediak-Higashi syndrome (CHS 1), Griscelli syndrome (GS 2), Hermansky–Pudlak syndrome (HPS) and X linked proliferative syndrome (XLP) are primary immune deficiencies having distinctive clinical features besides the recurrent primary HLH.2-4

However, HLH is, often, an acquired or secondary syndrome which can occur in all age groups. Infection-associated HLH could be triggered by various agents such as viruses of the herpes group, especially Epstein-Barr virus (EBV) and cytomegalovirus (CMV) or by no viral agents such as Leishmania. Acquired HLH could also be associated with malignant diseases, especially lymphomas and to autoimmune diseases.[2-3] It has rarely been described HLH secondary to inborn errors of metabolism such as Lysinuric protein intolerance (LPI), a rare metabolic disorder resulting from recessive-inherited mutations in the SLC7A7 gene encoding the cationic amino-acids transporter subunit y+LAT1. This pathology is characterized by protein-rich fluid intolerance with secondary urea cycle disorder. It is a multiorgan disease, that could lead to infiltrative lung disease, kidney failure or auto-immune complications. The phenotypic heterogeneity of LPI has resulted in various misdiagnoses.6-11

We report, herein, the case of 9-month-old boy investigated for a persistent HLH with very high hyperferritinemia. Throughout this case, we describe the atypical presentation and outcome of HLH and we insist on differential diagnosis of chronic HLH that must be kept in mind of specialists.

Report of the Case.

Case presentation and clinical history. M.K is a 9-month-old boy, born from a consanguineous marriage. He had been breastfed for seven months with normal growth. Since food diversification, he exhibited poor weight gain, developed recurrent diarrhea, hepatomegaly, and splenomegaly with pancytopenia, increased serum ferritin and lactate dehydrogenase (LDH) level. Hence, he was referred to the immune-hematologic unit, for hemophagocytic lymphohistiocytosis (HLH) suspicion.

Initial workup. Physical examination showed pallor, hypotonia, failure to thrive, liver and spleen enlargement. No fever was noted. The physical examination did not reveal other abnormalities. Urine bandlets showed proteinuria and microscopic hematuria. Laboratory findings (Table 1) showed pancytopenia with normochromic normocytic non-regenerative anemia; neutropenia, lymphopenia, and thrombocytopenia (14 mmol/l), high cholesterol (8 mmol/l) (Figure 1), elevated very low-density lipoproteins (VLDL) and low high-density lipoproteins (HDL). He had low fibrinogen (0.74 g/l), without other signs of disseminated intravascular coagulation, increased LDH (3200 U/l), low urea (1,29 mmol/l) and normal creatinine. Other routine biological tests were

| Table 1. Hematological findings at admission and during follow up before and after treatment. |
|---------------------------------------------------------------|
| **Test** | **Units** | **HGB** | **MCV** | **MCH** | **RTC** | **PLT** | **WBC** | **NP** | **LY** |
|----------|-----------|---------|---------|---------|---------|---------|---------|--------|--------|
|          |           | 11-15   | 75-82   | 23-31   | 40-80   | 150-400 | 8-12    | 3.5-6  | 3.5-5  |
| Before treatment |         | 5.1     | 75      | 24      | 84.7    | 48      | 4.19    | 1.22   | 2.12   |
| Day 30   |           | 6.4     | 75      | 25      | 51.8    | 43      | 3.25    | 0.88   | 1.69   |
| 1 month  |           | 6.6     | 77      | 24      | 44.6    | 86      | 13.02   | 6.03   | 4.47   |
| 5 months |           | 7.4     | 88      | 29      | 31.4    | 75      | 7.16    | 1.58   | 4.12   |
| 8months  |           | 7.7     | 83      | 26      | 24.3    | 57      | 5.24    | 1.58   | 2.78   |
| 12months |           | 7.9     | 83      | 26      | 31.1    | 29      | 2.14    | 0.73   | 0.94   |
| 16months |           | 7.1     | 92      | 26      | 26      | 91      | 4.52    | 1.72   | 1.95   |
| 19months |           | 8.9     | 74      | 24      | 30.2    | 131     | 5.60    | 1.90   | 2.40   |
| 24months |           | 9.9     | 91      | 27      | 11.7    | 132     | 2.99    | 1.99   | 1.84   |

*Hemoglobin, b mean corpuscular volume, c mean hemoglobin concentration, d reticulocytes, e platelets, f white blood cells, g neutrophiles, h lymphocytes.
normal. Blood and bone marrow smears showed no hemophagocytosis. Cerebrospinal fluid (CSF) exam showed no activated cells. Cerebral MRI was normal.

**Differential diagnosis and further investigations.**

These clinical features of Hemophagocytic lymphohistiocytosis (HLH) prompted performing other investigations looking for an acquired HLH. So a complete workup was made to rule out an infection, an autoimmune disease or malignancy: microbiological and autoimmunity tests were negative, and blood and bone marrow smears showed no blasts.

**Differential diagnosis and further investigations.**

A primary HLH was suspected. The patient had no EBV infection suggesting an XLP. FLH was thought to be the primary cause of HLH due to parental consanguinity, history of a cousin with the same signs died at the age of 4 months, in the absence of other evident causes. Nevertheless, perforin expression and degranulation test were regular. Other underlying primary immune deficiency was searched. Immunologic tests showed average immunoglobulin G, A and M levels, moderate global lymphopenia CD4, CD8, B and NK and no increased activated lymphocytes (Table 2).

**Final diagnosis.** Moreover, several atypical elements were noted in this HLH: absence of fever, hypotonia without neurological activation detected on the CSF exam and cerebral MRI, recurrent diarrhea, hematuria and proteinuria, very high cholesterol level, and not increased HLA-DR expression. All these manifestations beginning since food diversification oriented to lysinuric protein intolerance (LPI). In fact, other metabolic errors mimicking HLH similarly like lysosomal acid lipase deficiency, or galactosemia manifest in the first days of life or at lactation, and Gaucher syndrome.

---

**Table 2.** Immunologic tests at diagnosis.

| Test                        | Patient | normal  |
|-----------------------------|---------|---------|
| CD3(µl)                     | 945     | 2100-6200 |
| CD4(µl)                     | 678     | 1300-3400 |
| CD8(µl)                     | 487     | 620-2000 |
| CD19(µl)                    | 349     | 720-2600 |
| NK (µl)                     | 99      | 180-920  |
| HLA DR+/CD3+(%)             | normal 7% | -  |
| HLA DR+/CD4+(%)             | normal 7% | -  |
| HLA DR+/CD8+(%)             | normal 6% | -  |
| HLA DR+/Lymphocytes(%)      | normal 38% | -  |
| CD25 expression             | normal  | -      |
| Immunoglobulin G (g/l)      | 7.19    | 2.69-9.13 |
| Immunoglobulin M (g/l)      | 1.38    | 0.32-1.55 |
| Immunoglobulin A (g/l)      | 0.4     | 0.08-0.54 |
| Degranulation test          | Patient | Temoin |
| CD8 (%)                     | 70      | 73      |
| without OKT3                | 0.75    | 0.4     |
| OKT3 0.03mg/l               | 16.5    | 11      |
| OKT3 0.3mg/l                | 64      | 57      |
| OKT3 3mg/l                  | 89      | 78      |
| OKT3 30mg/l                 | 96      | 82      |
disease was excluded by absence of the typical cells in bone marrow and by a regular glucocerebrosidase activity in cultured fibroblasts.

Serum ammonium level was found increased at 112 UI/l (normal ≤70 UI/l). Metabolic tests showed an increased urinary excretion of orotic acid. The amino acid analyses from plasma and urine showed low plasma levels of cationic amino acids (CAAs) and increased urinary excretion of CAAs. Organic - acid analyses from urine at diagnosis showed increased urinary intermediary organic acids of the Krebs cycle (Table 3). This profile with low plasma levels of CAAs and increased urinary excretion, orotic aciduria and hyperammonemia is compatible with a defect in the y+LAT1 sub-unit of the cationic amino-acids transporter encoded by the SLC7A7 gene.

**Treatment and outcome.** Citrulin supplementation to 100 mg/kg/day was prescribed with protein intake limited to 0.8 g/kg/day. Liver and spleen enlargement decreased, hypotonia disappeared. The patient has gained 12 kg in two years. He needed repeated platelet and blood cell transfusions during the first month. Hematological disorders have gradually improved with persistent mild anemia not requiring further transfusions (Table 1). Ammonium, triglycerides, and cholesterol quickly fell to normal levels one month after treatment and are still in average ranges.

**Table 3.** Results of amino acid analyses from plasma and urine and results of organo-acids from urine.

|                  | Plasma amino-acids (µmol/l) | Urinary amino-acids (µmol/mmol creatinin) |
|------------------|-----------------------------|-------------------------------------|
|                  | Patient                     | Normal                             | Patient                      | Normal                      |
| Taurine          | 46                          | 11-168                             | 402                          | 12-159                      |
| Aspartic acid    | 20                          | 5_33                               | 13                           | 3_10                        |
| Hydroxyproline   | 4                           | <29                                | 0                            | ≤13                         |
| Thréonine        | 58                          | 59-135                             | 99                           | 15-62                       |
| Serine           | 133                         | 87-183                             | 285                          | 45-124                      |
| Asparagine       | 57                          | 19-71                              | 133                          | ≤32                         |
| Glutamic acid    | 82                          | 29-119                             | 59                           | ≤11                         |
| Glutamine        | 405                         | 362-606                            | 389                          | 62-165                      |
| Proline          | 128                         | 93-233                             | 21                           | ≤13                         |
| Glycine          | 308                         | 160-264                            | 810                          | 110-356                     |
| Alanine          | 140                         | 174-374                            | 196                          | 41-130                      |
| 2-amino butyric  | 8                           | 4_49                               | 75                           | ≤8                          |
| Citrulline       | 23                          | 14-42                              | 218                          | ≤7                          |
| Valine           | 109                         | 133-293                            | 25                           | 7_21                        |
| 1/2Cystine       | 22                          | 45-113                             | 89                           | 10_26                       |
| Methionine       | 16                          | 17-29                              | 0                            | 7_299                       |
| Isoleucine       | 35                          | 31-79                              | 7                            | ≤6                          |
| Leucine          | 64                          | 59-151                             | 10                           | 3_17                        |
| Tyrosine         | 36                          | 39-79                              | 68                           | 13-48                       |
| Phenylalanine    | 68                          | 36-64                              | 80                           | 3_31                        |
| Ornithine        | 8                           | 25-93                              | 392                          | ≤8                          |
| Histidine        | 75                          | 52-104                             | 281                          | 87-287                      |
| 3-methylhistidine| 2                           | ≤7                                 | 72                           | 22-57                       |
| Lysine           | 66                          | 85-241                             | 1408                         | 16-69                       |
| Arginine         | 43                          | 34-106                             | 602                          | ≤8                          |
| Total amino-acids| 1948                        | 2016-3088                          | 6408                         | 700-1465                    |

|                  | Organo-acids from urine (µmol/mmol de créatinine) |
|------------------|--------------------------------------------------|
|                  | Patient                      | Normal                         |
| Lactic acid      | 152                          | ≤76                            |
| Glycolic acid    | 50                           | ≤92                            |
| 3-hydroxypropionic acid | 0                    | ≤4                             |
| 3-hydroxybutyric acid | 455               | ≤99                            |
| 3-hydroxyisovaleric acid | 7                   | ≤35                            |
| Methylmalonic acid | 6                     | ≤9                             |
| 2-Ethylhydracrylic acid | 4                   | ≤12                            |
| Ethylmalonic acid | 73                           | ≤15                            |
| Succiniec acid   | 55                           | ≤97                            |
| Fumaric acid     | 31                           | ≤10                            |
| Glutaric acid    | 6                            | ≤11                            |
| A.Malic acid     | 124                          | ≤11                            |
Fibrinogen value normalized within 5 months. Serum ferritin and LDH fell later after six months giving place to a persistent hyperferritinemia around 2000 ng/ml and permanent increased LDH around 2000 UI/l (Figure 1). During follow up, 24 months of treatment, no further authentic HLH occurred.

Discussion. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammation caused by uncontrolled proliferation of activated lymphocytes and histiocytes. Often, HLH is an acquired syndrome. However, HLH can be primitive in children, underlying inherited immune deficiencies. An additional HLH cause, the hereditary metabolic diseases and especially HLH related to lysinuric protein intolerance (LPI), is more and more described. These unusual presentations are responsible for diagnosis delay of rare disorders for which early intervention may modify the clinical course.

According to revised haemophagocytic lymphohistiocytosis (HLH) 2004 diagnostic criteria our patient fulfills only four of eight criteria. So, the diagnosis of leaky HLH was kept. Other laboratory findings, which are considered to be of diagnostic value in HLH, were also identified in our patient: hepatic enzyme abnormalities, elevated LDH, elevated VLDL and low HDL. In fact, in these revisited criteria haemophagocytosis in bone marrow aspirate is not constant. Moreover, some patients enrolled in the International Registry of HLH do not fulfill all the diagnostic criteria. It is currently accepted that hyperferritinemia in LPI is associated with LPI-related HLH even though the other HLH criteria are not prominent. Therefore, most of the non-metabolic biomarkers of LPI are explained by an underlying chronic or quiescent HLH that can progress to active HLH with fever. The hepatosplenomegaly observed in LPI reflect HLH rather than the nutritional depletion of CAAs.

HLH related LPI described in our patient differs from HLH in FLH. In LPI, HLH is chronic and intermittent. The hyperferritinemia and high LDH are usually the only permanent findings. Our patient has never normalized his ferritin and LDH levels. However, in FLH all those abnormalities are reversible and normalized when patients went into remission. Then, fever, the most constant feature and typically prolonged in FLH related HLH, was absent in our patient. It has been described that fever is not a prominent finding in LPI related HLH. We suggest that patients with suspected HLH, based on the clinical syndrome, should undergo the functional screening that is now a standing point in the diagnosis of HLH and FLH. Based on those findings, the lack of any functional defect could be one more strong argument to evaluate LPI in a child with no fever, growth retardation, and lack of the typical dysfunction of FLH. Distinguishing features between FLH related HLH and LPI related HLH are summarized in Table 4. The phenotypic heterogeneity of LPI has resulted in various other misdiagnoses reported in the literature such as cases of LPI misdiagnosed as food protein-induced enterocolitis syndrome. The diagnosis of LPI was also made in a 5-year-old male child followed for 3 years for multiple fractures, idiopathic osteoporosis, and short stature in the absence of typical features of LPI. These unusual presentations are responsible for diagnosis delay of rare disorders for which early intervention may modify the clinical course.

Our patient, like most of LPI subjects, displayed, other hematological and immunological abnormalities including chronic and intermittent anemia, thrombocytopenia, neutropenia and moderate global lymphopenia. Signs of T-cells dysfunction are usually present whenever investigated in LPI. The most evocative element of LPI in our patient, calling into question the FLH, was the association of leaky HLH to other features such as failure to thrive, extreme hyperlipidemia, neurological and kidney involvement and the onset of manifestations since food diversification. Proteinuria and microscopic hematuria should be followed over time since it can develop Fanconi syndrome or end-stage renal disease requiring dialysis.

The diagnosis of LPI is based on the presence of, at least, four of the following findings: (1) low plasma levels of CAAs; (2) increased urinary excretion of CAAs; (3) orotic aciduria; (4) hyperammonemia generally mild with usual protein intakes, prevented by oral administration of citrulline; and (5) reduced intestinal absorption of CAAs after an oral loading test. The first four criteria were present in our patient. Nutritional imbalance of CAAs does not explain the aberrant
inflammatory and immune responses. The mutation of SLC7A7 gene strongly impairs arginine efflux through system y+L in LPI monocytes and macrophages. It has been suggested that this may have a role in the crosstalk between T lymphocytes and macrophage leading to a defect in lymphocyte cytotoxic activity that prevents the efficient removal of antigens and results in abnormal immune activation of CTLs and macrophages explaining HLH in LPI.

There have been rare case reports of HLH secondary to other inborn errors of metabolism. HLH was described in Wolman disease, a severe systemic disease manifesting in the first days of life with vomiting, diarrhea, failure to thrive, hepatosplenomegaly, jaundice, anemia, and thrombocytopenia. A neonatal onset with distinctive markers of the disease such as subcapsular adrenal calcification and the presence of cytoplasmic lipid-laden vacuoles on bone marrow smear indicate an assessment of leukocytic cholesteryl esterase activity on blood leukocytes. Biotinidase deficiency should also be considered as a differential diagnosis of patients fulfilling HLH criteria, especially in the presence of ketolactic acidosis and organic aciduria.

Three cases with organic acidemia who developed HLH during the course of metabolic disorder have been reported. All the patients presented with metabolic acidosis and ketosis and increased histiocytes, lipid-laden macrophages in bone marrow aspirate. It was reported a case of an infant with early-onset cobalamin C deficiency who presented with HLH with symptoms of feeding difficulty, hypotonia, lethargy, and seizures in the first month of life. Urine organic acid analysis, acylcarnitine profile, and plasma homocysteine could orient to the diagnosis which must be confirmed by specific tests. HLH has also been described in association with Gaucher disease. Features of Gaucher disease, which are common to HLH, include unexplained fevers and cytopenias, both of which are explainable by the inflammation mediated by macrophages. In our patient, the cultured fibroblasts enzyme assay...

| Table 4. Distinguishing features between Familial lymphohistiocytosis (FLHª) related HLHª and lysinuric protein intolerance (LPIª) related HLHª. |
| Mechanism of HLHª | Cytotoxicity/degranulation congenital defect | Impaired arginine efflux in monocytes and macrophages |
| Age at onset | Usually early onset (from birth to adulthood) | Typically, after food diversification |
| Fever | Nearly constant | May be absent |
| Hepatosplenomegaly | Nearly constant | Nearly constant |
| Associated signs | Usually an isolated HLHª | Multi-organ disease |
| Neurological involvement | Activation in CSN, (activated lymphocytes in CSF) | Hyperammonemic complications |
| Dyslipidemia | High triglycerides | Major combined hyperlipidemia, hyper LDL cholesterol |
| Hyperferritinemia, anemia, and thrombocytopenia | During HLH episode | Chronic |
| Bone marrow hemophagocytosis | Phagocytosis of erythrocytes and platelets by histiocytes | Participation of neutrophil precursors and exclusive phagocytosis of pyknotic polymorphonuclear leukocytes and acidophilic erythroblast nuclei. |
| HLH severity | Usually complete and severe HLHª | Usually leaky HLHª |
| Immunologic abnormalities | Perforin defect and/or negative degranulation test | No functional defect, possible lymphopenia, hypogammaglobulinemia |
| Immunosuppressive treatment | Mandatory, no spontaneous regression | Indicated only when life-threatening HLH despite dietary treatment and citrulline |
| Outcome | Free interval between two HLHª episodes | HLH features are quiescent and chronic |
| Prevention of relapses | Mandatory up to HSCT | Not indicated |

ª Hemophagocytic lymphohistiocytosis, familial lymphohistiocytosis, lysinuric protein intolerance, Cerebro-spinal fluid, Hematopoietic stem cell transplantation.
revealed normal glucocerebrosidase activity. These cases suggest that a careful metabolic workup should be performed, extending to more advanced tests than organic and amino-acid analyzes when facing to a pediatric patient with HLH especially if clinical features of the patient suggested a metabolic disorder including hypotonia, irritability, or mild developmental delay.

The persistent symptoms mimicking HLH in our patient must be carefully monitored since it can progress to a life-threatening condition. Immunosuppressive drugs should be considered in LPI only when there is a clear threat to life.[9, 14] It was reported that combined hyperlipidemia frequently seen in LPI requires a specific treatment with HMG-CoA reductase inhibitors.[26] However, hyperlipidemia disappeared quickly in our patient. Citrulline treatment does not improve all features in our patient. Large amounts of citrulline increase the intracellular synthesis of arginine and may further stimulate the immune cascade in reticular endothelial cells.[15] It has been suggested that lysine supplementation could be able to ameliorate the clinical symptoms of LPI that are not corrected by citrulline.[27]

In a child presenting HLH, a wide range of exams should be performed to rule out an infection, an autoimmune disease or malignancy, since most of these causes are treatable. If primary HLH is suspected, an underlying immune deficiency like FLH, GS, CHS, XLP, should be screened. However, metabolic diseases such as LPI must be kept in mind of specialists as a differential diagnosis of HLH, and a careful metabolic workup should be performed when facing to a pediatric patient with HLH especially if clinical features suggested a metabolic disorder. The lysinuric protein intolerance should be considered in the differential diagnosis of familial lymphohistocytosis, especially in the absence of fever and the association of atypical clinical and biological features to HLH including hypotonia, irritability, food intolerance, and renal involvement. We suggest that patients with suspected HLH, based on the clinical syndrome, should undergo the functional screening. The lack of any functional defect could be one more strong argument to evaluate LPI in a child with no fever, growth retardation, and lack of the typical dysfunction of FLH. An early diagnosis of LPI can prevent unnecessary intensive immunosuppressive therapy and bone marrow transplantation. LPI related HLH is often chronic and quiescent with permanent hyperferritinemia. However, it must be carefully monitored since it can progress to life-threatening HLH.

References:

1. Gholam C, Grigoriadou S, Gilmour KC, Gaspar H.B. Familial haemophagocytic lymphohistocytosis: advances in the genetic basis, diagnosis and management. Clinical and Experimental Immunology 2011; 163: 271-83. https://doi.org/10.1111/j.1365-2249.2010.04302.x PMid:21303357 PMCid:PMC308610

2. Ramachandran S, Zaidi F, Aggarwal A, Gera R. Recent advances in diagnostic and therapeutic guidelines for primary and secondary haemophagocytic lymphohistocytosis. Blood Cells Mol Dis 2017; 64: 53–57. https://doi.org/10.1016/j.bcmd.2016.10.023 PMid:28433836

3. Janka G.E. Familial and acquired hemophagocytic lymphohistocytosis. Eur J Pediatr 2007; 166 (2):95–109. https://doi.org/10.1007/s00431-006-0258-1 PMid:17151879

4. Immashuku S, Ueda I, Teramura T, Mori K, Morimoto A, Sako M, Ishii E. Occurrence of haemophagocytic lymphohistocytosis at less than 1 year of age: analysis of 96 patients. Eur J Pediatr 2005; 164 (5): 315–19. https://doi.org/10.1007/s00431-005-1636-9 PMid:15731905

5. Mehta RS, Smith RE. Hemophagocytic lymphohistiocytosis (HLH): a review of literature. Med Oncol 2013; 30(4):740. https://doi.org/10.1007/s11019-013-0740-3 PMid:24105023

6. Parenti G, Sebastio G, Strisciuglio F, Incerti B, Pecoraro C, Terracciano L, Andria G. Lysinuric protein intolerance characterized by bone marrow abnormalities and severe clinical course. J. Pediatr 1995; 126 (2):246–51. https://doi.org/10.1016/S0022-3476(95)70552-X

7. Duval M, Fenneau O, Doreau V, Fayé A, Emilie D, Yotnda P, Drapier JC, Schlegel N, Sterkers G, de Baulny HO, Vilmer E. Intermittent hemophagocytic lymphohistiocytosis is a regular feature of lysinuric protein intolerance. J Pediatr 1999; 134 (2):236-9. https://doi.org/10.1016/S0022-3476(99)70423-3

8. Tanner LM, Nanto-Salonen K, Ninnokson H, Jahnukainen T, Keskinen P, Saha H, Kananen K, Helantera A, Metso M, Limamuuo V, Huoponen K, Sinell O. Nephropathy advancing to end-stage renal disease: a novel complication of lysinuric protein intolerance. J Pediatr 2007; 150 (6):631–34. https://doi.org/10.1016/j.jpeds.2007.01.043 PMid:17517249

9. Güzel-Ozantürk A, Ozgül RK, Unal O, Hismi B, Aydin Hl, Sivri S, Tokatlı A, Coşkun T, Aksöz E, Dursun A. Molecular and clinical evaluation of Turkish patients with lysinuric protein intolerance. Gene 2013;521 (2): 293–5. https://doi.org/10.1016/j.gene.2013.03.033 PMid:23542076

10. Gupta S, Weitzman S. Primary and secondary hemophagocytic lymphohistocytosis: clinical features, pathogenesis and therapy. Expert Rev Clin Immunol 2010; 6 (1): 137–54. https://doi.org/10.1586/eci.09.58 PMid:20383897

11. Mauhin W, Habarou F, Gobin S, Servais A, Brassier A, Grisel C, Roda C, Pinto G, Moshous D, Ghalam F, Krug P, Delourt N, Pontouze C, Dubois S, Assouan M, Galmiche L, Bonnefont JP, Ottolenghi C, de Blic J, Amenou JB, de Loulay P. Update on Lysinuric Protein Intolerance, a Multi-faceted Disease Retrospective cohort analysis from birth to adulthood. Orphanet J Rare Dis 2017 ; 12(1):3. https://doi.org/10.1186/s13023-016-0550-8 PMid:28057010 PMCid:PMC5217205

12. Shinshu I. Hyperferritinemia in Hemophagocytic Lymphohistocytosis and Related Diseases. Pediatr Blood Cancer 2008; 51 (3):442–6. https://doi.org/10.1002/pbc.21623 PMid:18506755

13. Ariciò M, Janka G, Fischer A, Henter JI, Blanche S, Elinder G, Martinetti M, Rusca MP. Hemophagocytic lymphohistocytosis. Report of 122 children from the International Registry. PHL Study Group of the Histioocyte Society. Leukemia 1996; 10(2):197-203. PMid:8637226

14. Ogier de Baulny H, Schiff M, Dionisi Vici C. Lysinuric protein intolerance (LPI): A multi-organ disease by far more complex than a classic urea cycle disorder. Molecular Genetics and Metabolism 2012; 106 (11):12–7. https://doi.org/10.1016/j.ymgme.2012.02.010
15. Sebastio G, Sperandeo MP, Andria G. Lysinuric protein intolerance: reviewing concepts on a multisystem disease. Am J Med Genet C Semin Med Genet 2011; 157C(1):54-62. https://doi.org/10.1002/ajmg.c.30287 PMid:21308987

16. Maines E, Comberiati P, Piacentini GL, Boner AL, Peroni DG. Lysinuric protein intolerance can be misdiagnosed as food protein-induced enterocolitis syndrome. Pediatric Allergy and Immunology 2013; 24: 509–510. https://doi.org/10.1111/pai.12096 PMid:23772603

17. Posey JE, Burrage LC, Miller MJ, Liu P, Hardison MT, Elsea SH, Sun Q, Yang Y, Willis AS, Schlesinger AE, Bacino CA, Lee BH. Lysinuric Protein Intolerance Presenting with Multiple Fractures. Mol Genet Metab Rep 2014; 1: 176–183. https://doi.org/10.1016/j.ymgmr.2014.03.004 PMid:25419514

18. Barilli A, Rotoli BM, Visigalli R, Bussolati O, Gazzola GC, Gatti R, Dionisi-Vici C, Martellini D, Goffredo BM, Font-Llitjós M, Mariani F, Luissetti M, Dall’AstA V. Impaired phagocytosis in macrophages from patients affected by lysinuric protein intolerance. Mol Genet Metab 2012; 105(4):585-9. https://doi.org/10.1016/j.ymgme.2012.01.008 PMid:22325938

19. Barilli A, Rotoli B.M, Visigalli R, Bussolati O, Gazzola G.C, Kadija Z, Rodi G, Mariani F, Ruzza ML, Luissetti M, Dall’AstA V. In lysinuric protein intolerance system y+L activity is defective in monocytes and in GM-CSF-differentiated macrophages. Orphanet J Rare Dis 2010; 5:32. https://doi.org/10.1186/1750-1172-5-32 PMid:2110863 PMCID:PMC2999969

20. Rabah F, Al-Hashimi N, Beshlawi J. Wolman’s disease with secondary hemophagocytic lymphohistiocytosis. Pediatr Hematol Oncol 2014; 31(6):576-8. https://doi.org/10.3109/08880018.2014.920942 PMid:24933302

21. Taurisano R, Maiorana A, De Benedetti F, Dionisi-Vici C, Boldrini R, Deodato F. Wolman disease associated with hemophagocytic lymphohistiocytosis: attempts for an explanation. Eur J Pediatr 2014;173(10):1391-4. https://doi.org/10.1007/s00431-014-2338-y PMid:24844354

22. Kardas F, Patiroglu T, Unal E, Chiang SC, Blyceeson YT, Kendirci M. Hemophagocytic syndrome in a 4-month-old infant with biotinidase deficiency. Pediatr Blood Cancer 2012 ; 59(1) :191-3. https://doi.org/10.1002/pbc.23247 PMid:22605457

23. Gokce M, Unal O, Hismi B, Gumruk F, Coskun T, Balta G, Unal S, Cetin M, Kalkanoglu-Sivri HS, Dursun A, Tokafti A. Secondary hemophagocytosis in 3 patients with organic academia involving propionate metabolism. Pediatr Hematol Oncol 2012 ; 29(1) :92-8. https://doi.org/10.3109/08880018.2011.601402 PMid:21970506

24. Susan Wu, Ignacio Gonzalez-Gomez, Thomas Coates, Shoji Yano. Cobalamin C disease presenting with hemophagocytic lymphohistiocytosis. Pediatr Hematol Oncol 2005; 22(8):717-21. https://doi.org/10.1080/08880010500278871 PMid:16251179

25. Sharpe LR, Ancliff P, Amrolia P, Gilmour KC, Vellodi A. Type II Gaucher disease manifesting as haemophagocytic lymphohistiocytosis. J Inherit Metab Dis. 2009; 32 (1): S107-10. https://doi.org/10.1007/s10545-009-1091-2 PMid:19267217

26. Tanner LM, Numakoski H, Nanto-Salonen K, Simell O. Combined hyperlipidemia in patients with lysinuric protein intolerance. J Inherit Metab Dis 2010; 33 Suppl 3:S145-50. https://doi.org/10.1007/s10545-010-9050-3 PMid:2017788

27. Lukkarinen M, Nanto-Salonen K, Pulkki K, Aalto M, Simel O. Oral Supplementation Corrects Plasma Lysine Concentrations in Lysinuric Protein Intolerance. Metabolism 2003; 52(7): 935-8. https://doi.org/10.1016/S0026-0495(03)00089-1