Hematologic Findings of Inherited Metabolic Disease; They are More Than Expected

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Summary: Inherited metabolic diseases are pathologic conditions that generally develop as a result of impairment of the production or breakdown of protein, carbohydrate, and fatty acids. Early determination of hematological findings has a positive effect on the prognosis of metabolic diseases. Three hundred eighteen patients who were being followed-up within the previous 6 months at Department of Pediatric Nutrition and Metabolism, Gazi University, Turkey, were included in the study. The hematological findings were classified under 7 main groups: anemia of chronic disease, iron deficiency anemia, vitamin B12 deficiency anemia, hemophagocytosis, leukocytosis, and thrombocytosis. Nine hundred twenty-two hematological examinations of the 319 patients were included in the study, and 283 hematological findings were determined, 127 anemia of chronic disease, 81 iron deficiency anemia, 56 cytopenia, and 4 vitamin B12 deficiency anemia. Leukocytosis (n = 1), thrombocytosis (n = 5), and hemophagocytosis (n = 9) were also observed. It was determined that, although anemia of chronic disease and nutritional anemia are the most common hematological findings, these may be diagnosed late, whereas neutropenia, thrombocytopenia, pancytopenia, and hemostasis disorders may be diagnosed earlier. Our study is the most comprehensive one in the literature, and we think it would positively contribute to the monitoring and prognosis of congenital metabolic diseases.

Key Words: metabolic disease, anemia, neutropenia, thrombocytosis

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As the frequency of consanguineous marriages in Turkey is quite high, congenital metabolic diseases are also commonly encountered.[1,2] Metabolic diseases are pathologic conditions that generally develop as a result of impairment of the production or breakdown of protein, carbohydrate, and fatty acids in association with autosomal recessive genetic disorders. The most common congenital metabolic conditions are amino acid metabolism disorders. Hematological problems are some of the most frequently observed findings of congenital metabolic diseases. These may be seen together with other systemic findings or, sometimes, as the first and only diagnostic finding of disease. Early determination of hematological findings has a positive effect on the prognosis of metabolic diseases. However, there are a few studies about the incidence of hematological findings in congenital metabolic diseases.[3,4] This raises the question of whether we know the true incidence and its significance.[5] The hematological findings of congenital metabolic diseases were evaluated in the concept of these factors. Our study is the most comprehensive one in the literature, and we think it would positively contribute to the monitoring and prognosis of congenital metabolic diseases.

MATERIALS AND METHODS

Three hundred eighteen patients, who were being followed-up within the previous 6 months at Department of Pediatric Nutrition and Metabolism, Gazi University, Turkey, were included in the study. Patients' hematological findings were taken from Department of Pediatric Nutrition and Metabolism and hospital data-processing records. All procedures followed were in accordance with the ethical standards of the Helsinki Declaration. The study does not contain any studies with human or animal subjects that were carried out by any of the authors. The presented study was approved by Gazi University ethical committee with the number 08.07.2013/57. As the patients were in different age groups, hematological findings were compared with normal values for each patient's age group.[6] The hematological findings were classified under six main groups: anemia of chronic disease, iron deficiency anemia, vitamin B12 deficiency anemia, hemophagocytosis, leukocytosis, and thrombocytosis. Metabolic diseases were classified according to the textbook of Inborn Metabolic Diseases: Diagnosis and Treatment.[7]

RESULTS

One hundred fifty-one of the patients enrolled were female individuals and 167 were male individuals. Their ages ranged between 1 month and 63 years, with a median age of 2.4 years. Nine hundred twenty-two hematological examinations of the 319 patients were included, and 283 hematological findings were determined, 127 anemia of chronic disease, 81 iron deficiency anemia, 56 cytopenia, and 4 vitamin B12 deficiency anemia. Leukocytosis (n = 1), thrombocytosis (n = 5), and hemophagocytosis (n = 9) were also observed. Patients' hematological findings are shown in Table 1.

DISCUSSION

The most important factor in the diagnosis of congenital metabolic disease is suspicion. Otherwise different clinical conditions may be considered, particularly sepsis, and this may lead to delays in diagnosis and even to loss of life. Hematological findings are some of the most common

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TABLE 1. Hematological Findings of Patients

Metabolic Disease Type	N	Application Number	No. Hematological Findings	Chronic Disease Anemia	Iron Deficiency Anemia	Cytopenia	Vitamin B 12 Deficiency	Leukocytosis	Thrombocytosis	Hemophagocytosis
Tyrosine metabolism disorders	13									
Hereditary tyrosinemia type I	9	20	11	5	3	3				
Alkaptonuria	4	4	1		1					
Branched-chain organic acidurias/ acidemias	22									
Maple syrup urine disease	9	33	25	23		2				
Propionic aciduria	3	3	3	1		2				
Methylmalonic aciduria	8	8	8	5		3				
3-Methylcrotonyl glycinuria	2	2	1			1				
Hyperphenylalaninemia	20	51	15		11	1	1	1	1	
Transport defects of amino acids at the cell membrane	4									
Lysinuric protein intolerance*	3	14	12	2			1			9
Cystinuria	1	1								
Nonketotic hyperglycinemia	6	42	8		8					
Cerebral organic acid disorders and other disorders of lysine catabolism	10									
Glutaric aciduria type I	10	13	3	2	1					
Disorders of sulfur amino acid metabolism	4									
Homocystinuria	4	31								
Disorders of the urea cycle and related enzymes	7									
Argininosuccinate synthetase deficiency	4	4	1	1						
Arginase deficiency	1	1	1	1						
Ornithine transcarbamoylase deficiency	2	2	1	1						
Disorders in the metabolism of glutathione and imidazole dipeptides	5									
Prolidase deficiency	1	1								
Glutathione synthetase deficiency	4	4	2	2						
Biotin-responsive disorders	14									
Biotinidase deficiency	13	27	10	2	8					
Holocarboxylase synthetase deficiency	1	1	1		1					
Disorders of cobalamin and folate transport and metabolism	12	138	11	6	2	3				
Disorders of fructose metabolism	20									
Fructose-1,6-bisphosphatase deficiency	8	30	9	3	4				2	
Fructose intolerance	12	50	3		2				1	
The glycogen storage diseases and related disorders	36									
Glycogen storage disease type 1 A	12	21	18	16			2			

Metabolic Disease Type	N	Application Number	No. Hematological Findings	Chronic Disease Anemia	Iron Deficiency Anemia	Cytopenia	Vitamin B 12 Deficiency	Leukocytosis	Thrombocytosis	Hemophagocytosis
Glycogen storage disease type 1 B	1	7	7			7				
Glycogen storage disease type 3	10	10	6	6						
Glycogen storage disease type 4	1	1	1	1						
Glycogen storage disease type 6	1	1								
Glycogen storage disease type 9	1	1								
Glycogen storage disease type 2	7	15	8	7	1					
Glycogen storage disease type 5	3	3								
Disorders of galactose metabolism	9	28	6	4	2					
Dyslipidemias	15	40	15		15					
Disorders of cholesterol synthesis	4	20								
Disorders of sphingolipid metabolism and neuronal ceroid-lipofuscinoses	48									
Gaucher disease	13	19	14		3	11				
Acid sphingomyelinase-deficient Niemann-Pick disease	13	45	19	4		15				
GM 1 gangliosidosis	3	3	1	1						
GM 2 gangliosidosis	5	9	1		1					
Krabbe Disease	2	6	5	4		1†				
Fabry disease	11	61	17	7	10					
Metachromatic leukodystrophy	1	1	1	1						
Mucopolysaccharidoses and oligosaccharidoses	42									
Mucopolysaccharidoses	42	58	15	8	7					
Congenital disorders of glycosylation	2	2	1			1				
Cystinosis	4	15	4	4						
Peroxisomal disorders	3	10	10	3		6			1	
Disorders of mitochondrial fatty acid oxidation and related metabolic pathway	8	30	4	4						
Disorders of ketogenesis and ketolysis	8	30	3	2	1					
Disorders of pyruvate metabolism and tricarboxylic acid cycle	1	4								
Defects of the respiratory chain	2	2	1	1						
Total	319	922	283	127	81	56	4	1	5	9

*One of the patients died during hemophagocytosis.
†It developed due to sepsis.

findings of congenital metabolic diseases and sometimes assist in the diagnosis of metabolic diseases and can sometimes determine the severity of the disease. They may also develop during treatment, and, if overlooked, they may prevent the expected benefit being obtained from the treatment. Understanding of hematological findings accompanying congenital metabolic diseases will therefore be of great value in terms of clinical follow-up. This study discusses hematological findings seen in patients monitored in our hospital.

In this study, there were 283 hematological findings in 25 metabolic disease groups, with anemia of chronic disease being the most frequent. The most important cause of chronic anemia is the decreased protein stores caused by restricted diet or insufficient nutrition. Early diagnosis and commencement of specific diet and close monitoring are quite important for prevention.[7] Despite being the most frequent finding, it could hardly help in recognizing a metabolic disease.

Iron deficiency anemia was observed in 81 patients in 14 different diseases (Table 1). This might be either attributable to restricted diet[8–10] or to the fact that these diseases are seen during infancy. There is also another cause leading to iron deficiency in patients with familial hyperlipidemia. The apheresis set used for lipid apheresis applied to 1 group of these patients causes chronic blood loss because of the 30 to 50 mL blood remaining in every procedure that leads to iron deficiency anemia. Such patients must be observed closely from that perspective, and prophylactic iron therapy must be administered.[11] There are also similar iron-deficient patients, because of blood loss in our study group.

Restricted diet is reported also to cause vitamin B12 deficiency and associated megaloblastic anemia,[12] which was seen in 4 of our patients.

Hemophagocytic lymphohistiocytosis (HLH) is one of the most striking and alerting hematological findings in metabolic diseases. It is observed 9 times in our patients with lysinuric protein intolerance. Unfortunately, one of our patients died because of this condition. In addition to lysinuric protein intolerance, HLH could also be seen in metabolic diseases such as sulfatase deficiency, galactosemia, Gaucher disease, Pearson syndrome, and galactosialidosis. None of our patients with such diseases had an HLH attack within the study period. While the mechanism underlying HLH in metabolic disorders is still unclear, it is possible that increased intermediary metabolites might have caused impairment of the functions of natural killer cells or cytotoxic T lymphocytes.[13]

Pancytopenia can develop in association with hypersplenism in lysosomal storage (such as Gaucher disease and Niemann-Pick) and glycogen storage diseases in which splenomegaly is the main clinical finding.[14] As shown in Table 1, cytopenias were most frequent in these patients in our study. Neutropenia represents a special group within the cytopenias and is particularly seen in glycogen storage disease type 1C. This patient group benefits from granulocyte colony stimulating factor therapy.[15] The 1 patient with neutropenia in our study was a type 1C subject and is receiving granulocyte colony stimulating factor therapy.

Pancytopenia could also occur in patients with methylmalonic acidemia because of initial acidosis during the neonatal period, which prevents bone marrow proliferation.[16,17] In later periods, however, a restricted diet and particularly vitamin B12 deficiency also contribute to the condition. The hematological problems observed in the 8 patients with methylmalonic acidemia in our study were common in the attack period, and most severe forms were noticed during the newborn period. Another metabolic disease causing pancytopenia is propionic acidemia.[18–20] Increased propionic acid in propionic acidemia has a known inhibitor effect on erythroid and granulocyte-monocyte colonies, and therefore it exhibits an adverse effect on proliferation and maturation in the bone marrow.[21] Three patients in our study had propionic acidemia. Two of these had pancytopenia in the metabolic decompensation period.

The condition most commonly associated with thrombosis in congenital metabolic diseases is hyperhomocysteinemia.[22] No thrombosis was observed in any of the 4 patients with hyperhomocysteinemia in our study. This may be attributable to the patients' young ages and to regular follow-up. The five thrombocytosis cases observed in our study (Table 1) could not be related to the diseases and might be secondary to infections.

Hematological findings, and particularly cytopenias, are frequently seen in congenital metabolic diseases. Although anemia of chronic disease and nutritional anemia are the most common hematological findings, these may be diagnosed late, while neutropenia, thrombocytopenia, pancytopenia, and hemostasis disorders may be diagnosed earlier. Metabolic diseases must be considered in the evaluation of cytopenias, particularly in cases with an atypical cause that are resistant to treatment and have additional accompanying findings. Early diagnosis and treatment of hematological disorders can also have a positive impact on the prognosis of metabolic diseases.

REFERENCES

1. Ozalp I, Coskun T, Tokol S, et al. Inherited metabolic disorders in Turkey. *J Inherit Metab Dis*. 1990;13:732–738.
2. Tunçbilek E. Clinical outcomes of consanguineous marriages in Turkey. *Turk J Pediatr*. 2001;43:277–279.
3. Tavil B, Sivri Kalkanoglu HS, Coskun T, et al. Haematological findings in children with inborn errors of metabolism. *J Inherit Metab Dis*. 2006;29:607–611.
4. De Lonlay P, Fenneteau O, Touati G, et al. Hematologic manifestations of inborn errors of metabolism. *Arch Pediatr*. 2002;9:822–835.
5. Evangeliou A, Dafnis E, Perdikoyanni C, et al. Hematological abnormalities in inborn errors of metabolism—how frequent are they? The Cretan experience. *Pediatr Hematol Oncol*. 2002;19:581–585.
6. Lanzkowsky P. Hematologic reference values. In: Lanzkowsky P, ed. *Manual of Pediatric Hematology and Oncology*, 5th ed. London: Elsevier; 2010:970–980.
7. Saudubray JM, Van den Berghe G, Walter JH. *Inborn Metabolic Diseases*, 5th ed. Germany: Springer; 2012.
8. Greene CL, Lango N. National Institutes of Health (NIH) review of evidence in phenylalanine hydroxylase deficiency (phenylketonuria) and recommendations/guidelines for therapy from the American Colloge of Medical Genetics (ACMG) and Genetics Metabolic Dietitians International (GMDI). *Mol Genet Metab*. 2014;112:85–86.
9. Royston NJW, Parry TE. Megaloblastic anaemia complicating dietary treatment of phenylketonuria in infancy. *Arch Dis Child*. 1962;37:430–435.
10. Bodley JL, Austin VJ, Hanley WB, et al. Low iron stores in infants and children with treated phenyl ketonuria: a population at risk for iron-deficiency anemia and associated cognitive deficits. *Eur J Pediatr*. 1993;152:140–143.
11. Eminoğlu TF, Yenicesu I, Tumer L, et al. Lipid apheresis applications in childhood experience in the University Hospital of Gazi. *Transfus Apher Sci Dec*. 2008;39:235–240.
12. Harvey WB, Feigenbaum AS, Clarke JT, et al. Vitamin B12 deficiency in adolescents and young adults with phenylketonuria. *Eur J Pediatr*. 1996;155:145–147.

13. Gökçe M, Unal O, Hismi B, et al. Secondary hemophagocytosis in 3 patients with organic acidemia involving propionate metabolism. *Pediat Hematol Oncol*. 2012;29: 92–98.
14. Zimran A, Altarescu G, Rudensky B, et al. Survey of the hematological aspects of Gaucher disease. *Hematology*. 2005;10: 151–156.
15. Hurst D, Kilpatrick L, Becker J, et al. Recombinant Human GM-CSF treatment of neutropenia in gycogen disease -1b. *Am J Pediatr Hematol Oncol A*. 1993;15:71–76.
16. Dionisi–Vici C, Deodato F, Röschinger W, et al. Classical organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: Long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. *J Inherit Metab Dis*. 2006;29:383–389.
17. Carazza F, Blum D, Clerax A, et al. Erythroblastopenia associated with methylmalonic aciduria. Case report and in vitro studies. *Biol Neonate*. 1996;70:304–310.
18. Grünert SC, Müllerleile S, Silva LD, et al. Propionic acidemia: clinical course and outcome in 55 Pediatric and adolescent patients. *Orphanet J Rare Dis*. 2013;10:6.
19. Ozand PT, Rashed M, Gascon GG, et al. Unusual presentations of propionic acidemia. *Brain Dev*. 1994;16:46–47.
20. Rafique M. Propionic acidemia: demographic characteristics and complications. *J Pediatr Endocrinol Metab*. 2013;26:497–501.
21. Storck LC, Ambruso RD, Wallner SF, et al. Pancytopenia in propionic acidemia: hematologic evaluation and studies of hematopoiesis in vitro. *Pediatr Res*. 1986;20:783–788.
22. D'Angelo A, Selhub J. Homocysteine and thrombotic disease. *Blood*. 1997;90:1–11.