Dicle Tıp Dergisi / Dicle Med J (2022) 49 (2) : 264-270

www.diclemedj.org

Original Article / Özgün Araştırma

Retrospective Evaluation of Inborn Errors of Metabolisms in the Level III Neonatal Intensive Care Unit

Ibrahim Deger[1], Ibrahim Taş[2], Serhat Samancı[3]

1 Dicle University School of Medicine, Department of Pediatric, Division of Neonatology, Diyarbakir, Turkey

2 University of Health Sciences, Zeynep Kamil Women and Children Diseases Training and Research Hospital, Istanbul, Turkey

3 Diyarbakır Children Hospital, Department of Pediatric, Diyarbakir, Turkey

Received: 20.12.2021; Revised: 30.03.2022; Accepted: 31.03.2022

Abstract

Objective: Inborn errors of metabolisms (IEMs) are a heterogeneous group of disorders that can occur as a result of inherited or spontaneous mutations, are rare when considered alone, but have many diseases as a group. Although they are generally thought of as diseases of the neonatal period, 50% of these also occur outside the neonatal period, and some are not diagnosed until adulthood. The aim of this study is to examine the frequency, clinical and laboratory features of inborn errors of metabolism in the neonatal period.

Methods: The results of 60 patients who were diagnosed with IEMs as a result of the study, out of 1400 patients who were followed up and treated in the Children's Hospital Neonatal Intensive Care Unit between January 2018 and December 2020, were evaluated.

Results: In this study, it consisted of 60 cases, 30 (%50) of which were girls and 30 (%50) were boys (50%). The median age of the patients included in the study was 3 (1-25) days at admission, median weight was 3100 (1000-4000) g, and gestational week was found to be median 39 (27-40) weeks at admission. The most common complaints were feeding difficulty 43(72%), tachypnea 27 (45%) and vomiting 5 (8.3%). The most common laboratory findings were metabolic acidosis 39 (65%) and 36 (60%) hypoglycemia. There was a history of consanguinity in 46 (76.6%) cases, and a history of sibling death in 30 (50%). The mother had a history of abortion in 5 (8.3%) patients who did not have a history of sibling death. The most common diagnoses were Urea cycle disorder 13 (21.7%), organic acidemia 12 (20%), galactosemia 10 (16.7%) and amino acid metabolism disorders 9 (15%).

Conclusion: Inborn errors of metabolisms, which are a group of diseases that can occur in different spectrums with clinical, biochemical and genetic heterogeneity, should be kept in mind especially in regions where consanguineous marriages are high. In cases such as metabolic acidosis, which presents with nonspecific symptoms such as malnutrition, tachypnea and jaundice in the neonatal period and cannot be explained in laboratory examinations, care should be taken and they should be referred to centers for further investigation.

Keywords: Hyperammonemia, Inborn Errors of Metabolism, Newborn, Urea cycle defect.

DOI: 10.5798/dicletip.1128817

Correspondence / Yazışma Adresi: *Ibrahim Deger, Dicle University School of Medicine, Department of Pediatric, Division of Neonatology, Diyarbakir, Turkey e-mail: drdeger@gmail.com*

Üçüncü Basamak Yenidoğan Yoğun Bakım Ünitesinde Doğuştan Metabolik Hastalıkların Retrospektif Değerlendirilmesi

Öz

Amaç: Doğuştan metabolizma hastalıkları, kalıtsal veya spontan mutasyon sonucu oluşabilen, tek başına ele alındığında nadir olarak görülen ancak bir grup olarak çok sayıda hastalığın olduğu heterojen bir bozukluk grubudur. Genellikle yenidoğan döneminin hastalıkları olarak düşünülse bile, bunların %50'si yenidoğan döneminin dışında da ortaya çıkar ve bazıları yetişkinliğe kadar tanı konulamaz. Bu çalışmanın amacı, yenidoğan döneminde doğuştan metabolik hastalıkların sıklığını, klinik ve laboratuvar özelliklerini incelemektir.

Yöntemler: Ocak 2018-Aralık 2020 tarihleri arasında, Çocuk Hastanesi Yenidoğan Yoğun Bakım Ünitesinde takip ve tedavisi yapılan 1400 hastadan, çalışma sonucunda doğuştan metabolik hastalık tanısı konan 60 hastanın sonuçları değerlendirildi.

Bulgular: Olguların 30 (%50)'si kız ve 30 (%50)'si erkek olmak üzere 60 hastadan oluşmaktadır. Çalışmaya alınan hastaların başvuru sırasında median yaş 3 (1-25) gün, başvuru sırasında ağırlık median 3100 (1000- 4000) g, gestasyon haftası median 39 (27-40) hafta bulundu. En sık başvuru şikayeti, beslenme güçlüğü 43 (%72), taşipne 27 (%45) ve apne 16 (%27) idi. Laboratuvar bulgularından en sık metabolik asidoz 39 (65%) ve hipoglisemi 36 (60%) saptandı. Olguların 46 (%76.6)'sında akrabalık öyküsü, 30 (%50)'sinde kardeş ölüm öyküsü vardı. Kardeş ölüm öyküsü olmayan 5 (%8.3) hastada annenin abortus öyküsü vardı. En sık konulan tanılar Üre siklus bozukluğu 13 (%21.7), Organik asidemi 12 (%20), Galaktozemi 10 (%16.7) ve aminoasit metabolizma bozuklukları 9 (%15) idi.

Sonuç: Klinik, biyokimyasal ve genetik heterojenite ile farklı spektrumlarda ortaya çıkabilen bir hastalık grubu olan doğuştan gelen metabolizma bozuklukları, özellikle akraba evliliklerinin yüksek olduğu bölgelerde akılda tutulmalıdır. Yenidoğan döneminde beslenememe, taşipne ve sarılık gibi nonspesifik semptomlarla başvuran, laboratuvar incelemelerinde açıklanamayan metabolik asidoz gibi durumlarda dikkatli olunmalı ve ileri inceleme yapılan merkezlere yönlendirilmelidir.

Anahtar kelimeler: Doğuştan metabolizma hastalıkları, Hiperamonyemi, Üre siklüs defekti, Yenidoğan.

INTRODUCTION

Inborn errors of metabolism (IEM) are a heterogeneous group of disorders that can occur as a result of hereditary or spontaneous mutations[1]. These disorders include disturbances of metabolic pathways involved in the breakdown or storage of carbohydrates, fatty acids and proteins[2]. Although any IEMs are very rare, when considered as a group, they may occur at varying rates such as 1 in 1800-2500[3]. They are generally thought of as diseases of the neonatal period, however, 50% of IEMs present outside the neonatal period and some are not diagnosed until adulthood[2]. Most are acquired through autosomal recessive inheritance, rarely autosomal dominant inheritance and through X-linked inheritance. Depending on the underlying disorder, they are pathophysiologically divided into three groups[1].

Group 1: Disorders of Intermediary Metabolism (amino acids metabolism and transport, fatty acid oxidation and ketogenesis, carbohydrate metabolism and transport, disorders related to vitamins, peptide metabolism, mineral metabolism, mitochondrial energy metabolism)[1].

Group 2: Disorders of the Breakdown of Complex Molecules and Biosynthesis (purine and pyrimidine metabolism, lysosomal storage diseases, bile acid and heme metabolism, glycosylation, lipoprotein metabolism)[1].

Group 3: Disorders of Neurotransmitter Metabolism (glycine and serine metabolism, pterin and biogenic amine metabolism, gamma-aminobutyrate metabolism, pyridoxine-dependent or folinic acid-responsive seizures, sulfite oxidase deficiency)[1]. Rapid diagnosis and appropriate treatment of IEMs are directly related to morbidity and mortality in patients[1]. While morbidity and mortality may be prevented with early diagnosis and appropriate treatment methods in most of the disorders in Group 1 and Group 3, majority of the disorders

in Group 2 cannot be treated[1]. Although the clinical findings of these disorders are very variable, they may present with a wide range of signs such as poor feeding, tachypnea, dyspnea, apnea, vomiting, feeding intolerance, hypotonia, convulsions, symptoms of shock and sudden death[4]. IEMs should be considered more frequently in cases with a history of sibling death or parental consanguinity[4].

The aim of this study is to examine the frequency, clinical and laboratory features of inborn errors of metabolisms disorders.

METHODS

In this retrospective cross-sectional study, 1400 patients who were treated and followed-up with a pre-diagnosis of metabolic disorders in the Diyarbakır Children's Hospital Neonatal Intensive Care Unit between January 2018 and December 2020 were included; as a result of the study, the results of 60 patients diagnosed with metabolic disorders were evaluated. Information such as gender, birth weight, date of last menstrual period and gestational age compatible with the pregnancy ultrasound, maternal age, number of pregnancies, mode of delivery of the mother, history of sibling death, time of admission, clinical findings and parental consanguinity were obtained from the medical files of the patients. The tests, radiological examinations, genetic examinations and treatments performed after the patients were admitted to the intensive care unit were recorded. The last diagnoses of the patients were also recorded.

The study was approved by Dicle university Ethics Committee for noninterventional studies (approval date: 03.06.2021 / approval number: 313).

Statistical Analysis

For the statistical evaluation of the data, the IBM SPSS Statistics 21 (SPSS Inc., Chicago, IL, USA) software was used. For the comparison of the quantitative data following normal distribution, the Student's t-test was used, and for the quantitative data that did not follow normal distribution, the Mann-Whitney U test was used. Descriptive statistics for continuous quantitative variables were presented as median (interquartile range), and for categorical variables, as number of cases and percentage (%).

RESULTS

The cases consisted of 60 patients, 30 of whom were girls (50%) and 30 were boys (50%). The median age of the patients included in the study at the time of admission was found to be 3 (1-25) days, the median weight was found to be 3100 (1000-4000) g, and the median gestational age was found to be 39 (27-40) weeks. 34 (55.7%) of the cases included in the study were delivered by normal spontaneous vaginal delivery, and 27 (44.3%) were delivered by cesarean section. The median maternal age was 26 (19-40) years, the median number of pregnancies was 3(1-13). Demographic data are given in Table 1. The most common complaints were feeding difficulties 43 (72%), tachypnea 27 (45%), apnea 16 (27%) and. 46 (76.6%) of the cases had a history of parental consanguinity, and 30 (50%) had a history of sibling death. In 5 (8.3%) patients who did not have a history of sibling death, the mother had a history of abortus. The most common laboratory findings were metabolic acidosis 39 (65%) and 36 (60%) hypoglycemia. Hemodiafiltration was performed in 11 (18.3%) patients and peritoneal dialysis was performed in 5 (8.3%) patients included in the study. The most common diagnoses were Urea Cycle Defects(UCD) 13 (21.7%), Organic acidemia 12 (20%), Galactosemia 10(16.7%) and amino acid metabolism disorders 9 (15%). Among the diagnosed IEMs, UCDs, Galactosemia, Organic acidemia and other diseases were presented in Table 2. 78.4% of the patients were discharged after their clinical and laboratory findings improved. In patients who were diagnosed with metabolic disorders and received treatment, the mortality rate was found to be 13 (21.6%). According to the diagnoses of the patients who resulted in mortality, 5/13 UCD, 2/13 congenital lactic acidosis, 1/13 galactosemia, 5/13 organic acidemia were found.

Table 1: Demographic characteristics of patients diagnosed with inborn errors of metabolisms

Gender	***n(%)***
Male	30(%50)
Female	30(%50)
	Median (Min.-Max.)
Birth weight (g)	3100 (1000-4000)
Gestational age (weeks)	39 (27-40)
Mother's age	26 (19-40)
Number of pregnancies of the mother	3 (1-13)
Age at the time of admission (days)	3 (1-25)

Table 2: List of patients diagnosed with inborn errors of metabolism

Diagnosis	**n(%)**
Ure cycle disorders	**13 (21.7)**
Argininosuccinic aciduria	2
Carbamoyl phosphate synthetase 1 deficiency (CPS1)	2
N-acetylglutamate synthase (NAGS)	3
Citrullinemia type I	5
Ure cycle disorders unidentified	2
Organic acidemias	**12 (20)**
Methylmalonic Acidemia (MMA)	4
Organic acidemia unclassifiable	5
Propionic acidemia	3
Galactose Metabolism Disorder	**10 (16.7)**
Classic galactosemia	10
Amino Acid Metabolism Disorder	**9 (15)**
Phenylketonuria (PKU)	1
Maple syrup urine disease (MSUD)	4
Nonketotic hyperglycinemia (NKH)	4
Energy Metabolism Disorder	**6 (10)**
Congenital lactic acidosis	5
Mitochondrial disease	1
Glycogen storage disease (GSD)	**4 (6.7)**
Pompe disease (GSD II)	4
Fatty Acid oxidation disorders	**3 (5)**
Glutaric aciduria type 2	2
Unclassifiable Fatty Acid Oxidation Disorder	1
Other Metabolic diseases	**3 (5)**
Biotinidase deficiency	1
Transient hyperammonemia of the newborn	2

DISCUSSION

Recent advances in the diagnosis and treatment of IEMs have significantly improved the prognosis for many of these conditions[5]. This shows that pediatricians and subspecialists should be aware of the clinical manifestations of these disorders. Various guidelines have been published for the stabilization and emergency treatment of critically ill infants[5]. Alongside these approaches, additional evaluations and recognition of infants who will benefit from special treatment are facilitated.

Inborn errors of metabolic disorders may generally be considered in two broad categories as 1- Acute or progressive intoxication or encephalopathy disorders and 2- Energy deficiency disorders[5]. In the intoxication type, signs and symptoms result from the accumulation of toxic compounds proximal to the metabolic disorder[5]. Patients typically present with clinical signs of acute or chronic intoxication and progressive or recurrent metabolic disturbances after a symptom-free interval[3]. In the energy deficiency type, patients may have clinical signs from birth and may not have symptom-free intervals[5]. Almost all of the children with IEMs, especially those who have the intoxication type, appear normal at birth because toxic metabolites are removed from the placenta during the antenatal period through the mother's metabolism[4]. In our study, almost all of our patients had normal birth weight and normal gestational age (95% and 90%).

Although IEMs are rare diseases when considered individually, they are quite common when considered as a group of diseases[5]. The frequency of IEMs varies depending on the ethnic structure of the society, the rate of consanguineous marriages, the diagnostic tests used, newborn screening programs, developing technologies, increasing reporting rates and awareness level[6]. Tu et al[7]. found the incidence of İEM's as 1.1%. It was found to be 4.2% in our

study. We think that the higher rate of consanguineous marriages in our region and the laboratory tests, genetic diagnosis methods and technological advances provided in the diagnosis of metabolic disease in recent years play a role in these results.

Inborn errors of metabolisms can emerge at any time in life[1,2]. Findings frequently present in the neonatal period because the neonatal period is an important period of catabolism[2]. In our study, the median time of onset of symptoms was 2 (1-23) days, and the median time of admission was 3 (1-25) days. The fact that the time of onset of symptoms and the time of admission were so short may be due to the high level of awareness of the families and the high number of patients with a history of sibling death in our region. It is difficult to distinguish IEMs from other neonatal disorders, because the symptoms in the neonatal period are not specific and the patients usually present with symptoms that can be confused with neonatal sepsis, such as malnutrition, respiratory distress, convulsions, lethargy, vomiting, hypothermia, and seizures[4]. In our study, the most common symptoms were feeding difficulties, seizures, vomiting and decreased activity, which were consistent with the literature. Due to the fact that consanguineous marriages are common in our country and accordingly IEMs are more frequently seen, IEMs should definitely be considered in the differential diagnosis of newborn babies who do not have risk factors for infection.

Most IEMs present with symptoms of acute or chronic metabolic encephalopathy, including urea cycle disorders, organic acidemias, and certain amino acid metabolism disorders[3]. Therefore, appropriate laboratory tests for metabolic disorders should be performed in any infant presenting with these findings[3]. Although sepsis is the first thing to consider in a newborn presenting with these symptoms, IEMs should always be included in the differential diagnosis, especially in term infants who do not have specific risk factors[1].

While neonatal-onset UCDs usually present with hyperammonemia in the neonatal period, diagnosis from neurological findings has been reported more frequently in late-onset UCDs. In the study of Unsinn et al.[8], in which neonatal-onset UCDs were evaluated, it was reported that the most frequently seen UCD in Switzerland was citrullinemia. Among the studies conducted in our country, Tokatlı et al.[9] reported citrullinemia as the most common UCD, and Kalkan et al.[10] reported CPS-1 and ASL deficiencies as the most common UCDs. Kulalı et al.[4] reported the rate of UCDs to be 15.2%. Since consanguineous marriages are common in our region, UCDs are seen more frequently. In our study, UCDs were found to be the most common group of diseases. In the study, UCDs were present in 13 (21.6%) of 60 patients diagnosed with metabolic disorders. The most common condition was citrullinemia, which was detected in 5 patients, and the second most common condition was N-Acetylglutamate synthase (NAGS) deficiency.

Galactosemia is an IEM caused by the deficiency of galactose-1-phosphate-uridyltransferase (GALT), galactokinase and epimerase enzymes in galactose metabolism[11,12]. Its worldwide incidence was reported as 1/40000-1/8000012. Although the prevalence of classic galactosemia was found to be 1:48.000 according to the results of newborn screening programs, Bosch et al.[13] found that some newborn screening programs recorded a prevalence of 1:10.000 when erythrocyte GALT enzyme activity <5% of control activity and erythrocyte galactose-1-phosphate concentration >2 mg/dL were used as diagnostic criteria[13,14]. The frequency of classic galactosemia in Ireland was found to be 1:16.47615. In our country, where consanguineous marriages are common, the incidence of galactosemia was reported as

1/2377511. As in other metabolic disorders, the frequency of galactosemia is high in our region. Galactosemia was detected in 10 (16.7%) of 60 patients in our study.

Pompe disease or Glycogen Storage Disease type II is a metabolic disorder caused by the deficiency of the lysosomal acid α-glucosidase (GAA) enzyme[16]. There are two forms of the disease: early (infantile) type and late-onset (juvenile-adult) type[17]. This autosomal recessive disorder is seen 1 in 30.000 to 150.000, depending on the age of onset, ethnic origin and differences of the geographic regions[16]. In the infantile form, the enzyme level is less than 1% and the clinical findings are more severe[17]. In our study, Pompe disease was detected in 4 (6.6%) of 60 patients.

Classic phenylketonuria (PKU) is the most common inherited amino acid metabolism disorder in the world2. In our study, PKU was found in only one patient; we think that this was due to the fact that PKU was in the screening program and the patients were diagnosed earlier and therefore treated earlier.

Methylmalonic acidemia (MMA), which is among organic acidemias, is an autosomal recessive disorder and its frequency is not definitively known in Turkey; it is normally formed by isoleucine, valine, threonine, methionine, and from propionic acid through methylmalonyl CoA racemase and methylmalonyl CoA mutase in the pathway of cholesterol catabolism[18]. In methylmalonyl CoA mutase or cofactor deficiency, methylmalonic acid and its precursors accumulate in body fluids and have a toxic effect on the central nervous system, bone marrow and kidneys[18]. Propionic acidemia is an autosomal recessive disorder caused by the accumulation of propionic acid in the blood resulting from the dysfunction of the propionyl-CoA carboxylase (PCC) enzyme[18]. In the study of Kulalı et al.[4], organic acidemia was found to be 15.2%, while in our study it was found to be 20%.

Maple syrup urine disease (MSUD) is an autosomal recessive metabolic disorder resulting from a genetic defect in the metabolism of branched-chain amino acids, with a frequency of approximately 1:185.000-940.00019. In the study of Kulalı et al.[4], the frequency of MSUD was found to be 6.6%, similarly, 4 (6.6%) patients were diagnosed with MSUD in our study.

Delay in the diagnosis of IEMs in children causes progressive neurological damage and death. In the study of Dionisi et al.[20], the mortality rate was determined as 25.2%, and in the study of Tu et al.[7], it was determined as 50%. In the study of Kulalı et al.[4], the total mortality was found to be 33.3%. In our study, the mortality rate was found to be 21.6%.

Limitations of the Study

Our study has some limitations. Some analyses are lacking due to the retrospective character of the study. This study was a single-center study conducted with a limited number of participants, in which the diagnoses of the patients were examined but the results regarding long-term postnatal follow-up were not evaluated.

CONCLUSION

In conclusion, Inborn errors of metabolisms are a group of diseases that may occur in different spectrums with clinical, biochemical and genetic heterogeneity. In our country and especially in regions like our region where there is a high rate of consanguineous marriages, it is important to be careful in terms of IEMs in conditions that cannot be explained in laboratory examinations such as metabolic acidosis, which presents with nonspecific symptoms such as malnutrition, tachypnea and jaundice in the neonatal period.

We believe that our study may provide convenience to pediatricians and neonatologists in terms of awareness of Inborn

errors of metabolisms, which are often among neonatal period morbidities and mortalities, in order to quickly consider these disorders in newborns and to diagnose the ones that require urgent intervention. However, we think that more extensive studies, in which higher number of patients are included, are necessary.

Ethical Committee Approval: The study was approved by Dicle university Ethics Committee for noninterventional stusies (approval date: 03.06.2021 / approval number: 313).

Financial Disclosure: No financial support was received.

Declaration of Conflicting Interests: There is no conflict of interest

REFERENCES

1. Stenton SL, Kremer LS, Kopajtich R, et al. The diagnosis of inborn errors of metabolism by an integrative "multi-omics" approach: A perspective encompassing genomics, transcriptomics, and proteomics. J Inherit Metab Dis. 2020; 43(1): 25-35.

2. Jeanmonod R, Asuka E, Jeanmonod D. Inborn Errors Of Metabolism. 2021. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

3. Brunetti-Pierri N, Parenti G, Andria G. Inborn errors of meta¬bolism. In Buonocore G, Bracci R, Weindling M (eds). Neonatology: A Practical Approach to Neonatal Diseases. Italia: Springer. 2012: 949-66.

4. Kulalı F, Köse M, Çelik TC, et al. Inborn Errors of Metabolism: A Three-Year Experience. Journal of Dr. Behcet Uz Children's Hospital. 2019; 9(2): 143-8.

5. Sutton VR. Inborn errors of metabolism: classification. UpToDate, 2017. Available from: https://www.uptodate. com/contents/inborn-errors-of-metabolism-classification.

6. Mak CM, Lee HH, Chan AY, et al. Inborn errors of metabo¬lism and expanded newborn screening: review and update. Crit Rev Clin Lab Sci. 2013; 50: 142-62.

7. Tu W, He J, Dai F, et al. Impact of inborn errors of metabolism on admission in a neonatal intensive care unit-a prospective cohort study. Indian J Pediatr. 2012; 79: 494-500.

8. Unsinn C, Das A, Valayannopoulos V, et al. Clinical course of 63 patients with neonatal onset urea cycle disorders in the years 2001-2013. Orphanet J Rare Dis 2016; 11: 116.

9. Tokatli A, Coskun T, Ozalp I. Fifteen years' experience with 212 hyperammonaemic cases at a metabolic unit. J Inherit Metab Dis 1991; 14: 698-706.

10. Kalkan Uçar S, Canda E, Köse M, et al. Presentation and management of classical urea cycle disorders: Lessons from our experience. Journal of Dr. Behcet Uz Children's Hospital. 2016; 6: 89-96.

11. Atik SU, Gürsoy S, Koçkar T, et al. Clinical, molecular, and genetic evaluation of galactosemia in Turkish children. Turk Pediatri Ars. 2016; 51(4): 204-9.

12. Berry GT, Walter J, Fridovich-Keil JL. Chapter 6; Disorders of Galactose Metabolism. In: Saudubray JM, Baumgartner MR, Walter J (Eds). Inborn Metabolic Diseases Diagnosis and Treatment, 6th Edition. Heidelberg: Springer Berlin; 2016: 139-46.

13. Bosch AM, Bakker HD, Wenniger-Prick LJ, et al. High tolerance for oral galactose in classical galactosaemia: dietary implications. Arch Dis Child. 2004; 89(11): 1034-6.

14. National Newborn Screening and Genetics Resource Center. National newborn screening status report. 2014.

15. Coss KP, Doran PP, Owoeye C, et al. Classical galactosaemia in Ireland: incidence, complications and outcomes of treatment. J Inherit Metab Dis. 2013; 36: 21–7.

16. Van der Ploeg AT, Reuser AJ. Pompe's disease. Lancet 2008; 372: 1342–53.

17. Fuller DD, ElMallah MK, Smith BK, et al. The respiratory neuromuscular system in Pompe disease. Respir Physiol Neurobiol. 2013; 189: 241–9.

18. Baştuğ O, Öztürk MA, Korkmaz L, et al. Pansitopeni ile Başvuran Metilmalonik Asidemi: Olgu Sunumu. Medical Journal of Bakirkoy, 2018: 14(1).

19. Ogier de Baulny H, Saudubray JM. Branched-chain organic acidurias. Semin Neonatol 2002; 7(1): 65-74.

20. Dionisi-Vici C, Rizzo C, Burlina AB, et al. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. J Pediatr. 2002; 140: 321-9.