Some of Congenital Metabolic Diseases in the Animals and in the Human: Review

Hayvanlarda ve İnsanlarda Bazı Doğumsal Metabolik Hastalıklar

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ABSTRACT First example of congenital metabolic diseases (CMD) is alkaptonuria which was identified in 1902. CMDs were mostly followed by pediatricians because of the age of onset. These diseases occurring because of quantitative or functional insufficiency of enzymes, which regulate chemical processes of the body, are not problems just peculiar to the human being. Many genetically defective sick animals, sorted out of the environment previously, are domesticated at the present time; thereby they find chance to live in sheltered environments. These animals could come into being not only as a result of natural mutations; but they may be formed intentionally in the laboratory in order to develop diagnosis and treatment methods for genetic disorders among the people. Identifying CMDs appearing among the animals and understanding the frequency of them may contribute to development of new treatment and diagnosis methods. Cooperation of veterinarians and medical doctors in this topic will give great acceleration to advance of field of metabolism.

Key Words: Metabolism, inborn errors; animals, domestic; diagnosis; animals, laboratory

ÖZET İlk doğumsal metabolik hastalık (DMH) örneği, 1902 yılında tanımlanan alkaptonüridir. DMH'ler başlangıç yaşı nedeni ile daha çok çocuk doktorları tarafından izlenmiştir. Vücudun kimyasal işlemlerinin düzenlenmesini sağlayan enzimlerin miktar veya fonksiyon olarak yetersizliği sonucu oluşan bu hastalıklar sadece insanlara özgü bir sorun değildir. Doğada daha önce ortamdan ayıklanan genetik kusurlu birçok hasta hayvan bugün evcilleştirilip korunaklı ortamlarda yaşama şansı bulabilmiştir. Bu hayvanlar doğal mutasyonlar sonucu oluşabildiği gibi, insanlardaki genetik bozuklukların tanı ve tedavi yöntemlerini geliştirmek amacı ile laboratuvarda istemli olarak da oluşturulabilmektedir. Hayvanlarda DMH'lerin tanınıp sıklığının anlaşılması yeni tedavi ve tanı yöntemlerinin geliştirilmesine katkıda bulunabilir. Veterinerlerin ve tıp hekimlerinin bu konuda ortak çalışması, metabolizma bilim dalının ilerlemesine daha büyük bir hız kazandıracaktır.

Anahtar Kelimeler: Metabolizma, doğumsal bozukluklar; hayvanlar, evcil; tanı; hayvanlar, laboratuvar

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Congenital or genetic metabolic diseases started to attract attention firstly in 1902 when Archibald Garrod identified "alkaptonuria-" which is an amino acid metabolism disorder. More than 50 years passed from the time Garrod observed that urine colour changes according to the dietary content and the disease passes through an autosomal recessive inheritance until the time when enzyme responsible for the disease was showed. La Du et al. established the enzymatic diagnosis just in 1958 by indicating that Homogentisic acid is responsible for this disease. Showing the place of the genetic problem became possible 40 years later.[1] As the speed of enzyme and gene

studies increases in medicine, these durations became shorter. As a result, more than 5000 congenital metabolic diseases (CMDs) have been identified in the present time.[1] These diseases have been published firstly in books under the editorship of Dr. Victor A. McKusick since 1960. As from 1995, they have been regularly updated and published on the internet]Online Mendelian Inheritance in Man (OMIM)].[1,2] Studies similar to the OMIM classification have been conducted on the internet for animals for more than 30 years.[1-8] Patterson, Jezyk et al. from University of Pennsylvania Laboratory Genetic Metabolic Diseases identified more than 1000 CMDs in cats and dogs (Online Mendelian Inheritance in Animals, http://www.omia.angis.org.au).[5] University of Cambridge published the data for dogs on internet (http://www.vet.cam.ac.uk).[1,5] More than 50 diseases were identified by Philadelphia study group. Findings give rise to thought that CMDs are not as rare as it is thought in the animals. Coupling breeds having close genetic characteristics particularly for the sake of obtaining a pure race increases the likelihood of appearance of genetic diseases. Being aware of clinical findings and diagnosis examinations about CMD will be the first step to establish a diagnosis and prevent the development of unhealthy generations.[1,4-8]

As in all diseases, CMD approach also starts with detailed history.[8,9] A well-received differential story gives many clues in the diagnosis. Details of deaths, similar disease histories and pregnancy and birth information which cannot be explained in the first ages are learnt through questioning which covers three generations.[8]

Symptoms in the newborns regarding CMDs generally start to emerge in a couple of days or weeks following the birth. There are also exceptions for that. Findings can start to appear intrauterin or in the adult period. Even though the clinical picture is multifarious, metabolic diseases should be suspected in the presence of lethargy, absence of suckling, vomiting, tachypnea (for compensation for metabolic acidosis), cardiac shock and convulsions. Signs of disease will be more serious if appropriate and emergency treatment is not conducted; and stupor, coma, changes in tone (hypotonia, hypertonia), posture (opistotonus) and movement (licking oneself, swallowing, myoclonus) changes, apnea and sleepiness appear.[8,9] A more serious response which cannot be explained to a mild infectious disease such as hypoglycemia, convulsion and the formation of coma are important clues for CMD.

Dysmorphy, corneal haze, coarse facial appearance, dysostosis multiplex, a characteristic body odor, hepatosplenomegaly, hypertrophic or dilated cardiomyopathy, neuromotor development delay and hypotonia are important data in differential diagnosis in terms of CMD.[9,10] Dysmorphy can be apparent in the birth; however, changes can occur in phenotype in the course of time in spite of normal delivery. While intrauterine exposure is considered first in dysmorphic babies, subsequent dysmorphy needs to be examined in terms of storage diseases. Particularly peroxisomal diseases are thought of in the presence of dysmorphic newborns. Many lysosomal storage diseases were identified in particularly cats and dogs through skeletal deformities and ocular findings.[7,10-14] Moreover, histopathological, biochemical, molecular diagnosis of those were established; and gene therapy studies could be conducted on some of them.[7,11,12,15,16]

Cooccurrence of abnormal ocular findings and CMD is frequent. It can appear as an early sign in the first month of life in cases of lens dislocation, homocystinuria, molybdenum co-factor deficiency, and sulfide oxidase deficiency. Retinal degenerative changes are generally seen together with peroxisomal diseases. Corneal haze and glaucoma are other eye symptoms which can appear together with CMD. When CMD is suspected, careful eye examination is of importance. Metabolically sick dogs with eye problems were defined in the literature.[9,10,12]

In the laboratory evaluation, diagnosis initiative is started with basic metabolic screening tests in the presence of suspicious findings (Table 1). Hyperammonemia, hypoglycemia, metabolic acidosis, the presence of ketones in the urine makes think of CMD. If there is a picture like Reye syndrome (nonspecific hepatic encephalopathy, hypoglycemia), urea cycle, gluconeogenesis, fatty acid oxidation, respiratory chain or organic acid metabolism disorders may be the reasons lying behind.[9,17,18] Among CMD findings, hyperammonemia is the most im-

TABLE 1: Routine laboratory evaluation.[10]

Finding	Disease
Macrocytic anemia	Folic acid + cobalamin metabolism disorders
Reticulositosis	Glycolysis disorders, disorders of gamma-glutamyl cycle
Vacuolized lymphocytes	Lysosomal storage diseases
High alkaline phosphatase	Bile acid synthesis defects
Low cholesterol	Sterol synthesis disorders, lipoprotein disorders
High CK	Mitochondrial disorders, fatty acid oxidation disorders, GSD, glycolysis disorders, muscle AMP deaminase deficiency, the dystrophinopathies
High alpha-fetoprotein	Ataxia-telangiectasia, tyrosinemia
Increase in uric acid	GSD, purine metabolism disorders, fatty acid oxidation disorders, mitochondrial diseases
Low uric acid	Purine metabolic disorders, the molybdenum cofactor deficiency
Highness of iron and transfer	Peroxisomal diseases
Increase in copper	Peroxisomal diseases
Low copper and ceruloplasmin	Wilson disease, Menkes disease, aceruloplasmin
Hypothyroidism, hypoparathyroidism	Mitochondrial diseases, CDG syndrome

portant one because of the acute encephalopathy. In case of high ammonia, encephalopathy findings can be seen in different levels such as nausea, vomiting, lethargy and coma. Urea cycle disorders and organic acidemias should be primarily investigated in the presence of serious hyperammonemia. Vitamin B_{12} metabolism depended hyper ammoniemia, neurological problems and methylmalonic acidurias were identified in the animals.[1] Other rare organic acidurias were identified particularly in the dogs.[17-19] In organic acidemias, an increase in plasma lactate can be seen because of the secondary interaction of these metabolites with coenzyme A metabolism besides original organic intermediate metabolites. Neutropenia and thrombocytopenia can be seen; and sepsis can be added to the clinical picture. Since inflammatory disease provides pathological findings in some CMDs or tests provide pathological findings in other stress situations, it may be necessary to repeat the test if the suspicion continues in the diseases in spite of the negative result.

In CMD, central nervous system, liver, heart, muscle, kidney, skeletal system and eyes are frequently affected. Particularly tubular dysfunction or stone formation is identified as most frequent complaint in involvement of the kidneys. Hyperoxaluria, prolinuria, hydroxyprolinuria, cystinuria, xanthinuria and uric aciduria were identified as causes of kidney stones in cats and dogs.[1,20,21]

Pyruvate metabolism or respiratory chain defects could lead to primary lactic acidosis creating severe metabolic acidosis. There is no other clue in urinary organic acid analysis. Lactate/ pyruvate rate should be investigated by evaluating plasma pyruvate level and lactate level simultaneously. Cardiac, cerebral involvement findings and encephalopathy episodes were identified in different dog breeds because of the mitochondrial disease.[1,9,21-24]

Clinical samples are available in animals for glycogen storage diseases which are one of the problems about synthesis and utilization of carbohydrates on metabolic pathway before the mitochondria, which lead to energy deficiency, and which are also classified as a storage disease.[17,22,24]

DIAGNOSIS AND TREATMENT APPROACH TO CONGENITAL METABOLIC DISEASES

The patient thought to have CMD through medical history and clinical findings should be primarily subjected to a physical examination to determine in which disease group he/she is in; and basal and, if necessary, special examinations should be planned.

Clinical findings can come about as intoxication table (hyperammonemia without ketonuria, hyperammonemia together with or without ketoacidosis); lack of energy table (together with lactic

acidosis, without lactic acidosis); table of storage, hypoglycemia or liver involvement (Table 1). Basal tests are taken according to the clinical findings (Table 2); and patients are oriented to further examinations according to the results.[5,9,25]

Emergency treatment should be started when organic acidemia and urea cycle disorders are suspected. Tests for differential diagnosis should be finalized within 48-72 hours. Appropriate and efficient treatment conducted until confirmation time of the diagnosis saves lives and prevents sequellae. In the first place, accumulation of ammonia or pathological metabolite should be prevented. To this end, protein intake is immediately stopped.

Hemodialysis is administered to the severely ill newborn with hyperammonemia; in this way, accumulated toxin is removed. If the patient is in a coma or connected to the ventilator, or if he/she has a brain edema, the patient should be subjected to emergency dialysis before the medical treatment. After removing the toxic substance, second target is to prevent catabolism. Primarily intravenous glucose is launched. If there are urea cycle disorders, intravenous lipid is started. No protein should be given until the diagnosis is established.

When organic acidemia is suspected, vitamin B_{12} should be started with 1 mg intra muscular. It is efficient in the form of methylmalonic acidemia which is responsive to the B_{12}. Patients with multiple carboxylases deficiency should be given 10 mg oral biotin. If acidosis is available, intra venous bicarbonate is administered.[26-28]

Hypoglycemia carbohydrate metabolism may be associated with fatty acid oxidation disorders or protein intolerance. The best-known type of it is hepatic glycogen storage disease (GSD). Release of glu-

TABLE 2: Diagnostic tests for congenital metabolic diseases.[10]

Uriner	Color, smell
	Bar tests
	Ketonuria (pathological in newborns)
	Alkaline pH (if >5 separate it from renal tubular acidosis)
	Special tests
	Sulfide test
	Reducing agent
	Ferric chloride 3 test
	Dinitrophenyl hydrazin test
	Electrolytes
	Na, K
	Organic acids, other special tests
Blood	Complete blood count
	Anemia, pancytopenia, granulocytopenia, thrombopenia
	Biochemical tests
	Electrolytes (adrenogenital syndrome)
	Blood sugar
	Liver function tests
	Uric acid
	Ca, P
	Blood gases, acid-base status, anion gap
	Ammonia, lactate (higher pyruvate, ketones, perchloric acid extraction)
	Amino acids (plasma)
	Emergency carnitine (Guthrie-card), carnitine level
Other tests	ECG, ECHO, cranial ultrasound
	Plasma taken in the acute phase, CSF; keep urine in the refrigerator

cose from glycogen is defective in the prolonged fasting. Hypoglycemia, hepatomegaly, and lactic acidosis are apparent findings of GSD.[9] Most of fatty acid oxidation disorders (FAO) give early finding with the hypoglycemia. When glycogen stores get empty and fatty acids start to be needed in prolonged fasting, hypoglycemia problems becomes evident for GSD and FAO. Since acetyl-CoA production decreases in spite of hypoglycemia development, ketone production is impaired. Even though just a limited number of ketones are produced, typically, non-ketotic hypoglycemia develops. Hypoglycemia can be seen by itself or together with other biochemical disorders associated with Reye syndrome such as hyperammonemia, metabolic acidosis, and liver dysfunction. Hepatomegaly can occur. That kind of newborn must never go hungry. Secondary carnitine deficiency is seen in FAO as a result of excessive excretion of acylcarnitine in the urine. Urine organic acids, serum carnitine evaluation are important in FAO differential diagnosis at the beginning. These tests are adequate for MCAD diagnosis. However, enzymatic diagnosis can be needed for some FAOs. During the treatment, sufficient glucose should be provided through a frequent feeding in such a way that would prevent the hypoglycemia; fatty acid group which cannot be metabolized in the diet is reduced, and carnitine support is provided.

Most of patients with lipid storage diseases (GM_1-gangliosidosis tip I, Gaucher disease, Niemann-Pick disease, Wolman disease) are born with normal appearance; and hepatosplenomegaly becomes apparent in early months of the life. Hepatomegaly can be seen in GSDs in the newborn period. Most of mucopolysaccharidoses such as Hurler and Hunter syndromes and mucolipidosises such as GM_1-gangliosidosis or I-cell disease are identified with coarse face, hepatosplenomegaly, skeletal anomalies and hernias in later period. Glucuronidase deficiency (mucopolysaccharidosis type VII) may give finding in newborn period. Findings are available in birth in infantile sialidosis. Sialidosis in utero can occur with severe hydrops fetalis. When these diseases are suspected, screening tests should be made for oligosaccharides and mucopolysaccharides. These tests help the diagnosis. However, as negative result does not leave out the diagnosis, wrong-positive results can be seen in the newborn. Lysosomal storage diseases must be differential diagnosis by enyzmatic study in leukocytes or skin fibroblast culture.[5,25-28]

Showing skeletal deformities through radiological examinations provide important clues for diagnosis of lysosomal storage diseases. Neuroradiological evaluations (cranial computed tomography, cranial magnetic resonance imaging and spectroscopy) provide information about organic acidemias, storage diseases, mitochondrial disorders, fatty acid oxidation disorders. Abdominal ultrasound gives finding about liver, spleen, kidney and urinary tracts, storage diseases and aminoaciduria-induced stone diseases.

CMD which are frequently seen thoroughout the world were taken into the scope of screening for all newborn babies among the human beings.[9,26-28] Amino acid metabolism disorder called phenylketonuria is screened almost all around the world. In addition, if there is a disease known to be identified in the family beforehand, there is even possibility to diagnose the disease intrauterine.[5,9] Postmortem blood, muscle tissue, liver tissue, urine, cerebrospinal fluid samples of patients who were suspected to have CMD but who died before being diagnosed with a disease can be taken, and the examination can be maintained to a finish.[9] Diseases frequently seen among the animals according to the breeds are screened in terms of metabolic diseases.[5]

DISCUSSION

In Turkey, most of the basal examinations are conducted in faculties of veterinary science. However, examination of free carnitine and carnitine esters in blood via tandem mass spectrometry, examination of organic acids in the urine via gas spectrometry, quantitative amino acid analysis in blood, urine, and if necessary, in cerebrospinal fluid which are all special metabolic tests can be conducted in children's metabolic disease labs of medical faculties. Advanced enzymatic and molecular examinations can be conducted in children's metabolic and genetic laboratories. However, it is necessary to constitute adequate data base particularly in borderline cases

so as to create normal range of value for animals. Moreover, it may be necessary to take permission in order for these laboratories to examine the samples taken from the animals. Real solution is the launch of these studies by scientists in biochemistry departments of faculties of veterinary, who are interested in the topic.

Clinical veterinarians, veterinary pathologists and radiologists should refresh their knowledge about the topic so as not to skip any case. This is because, a new disease is identified and new treatment methods are developed everyday. A bit of attention and information can save lives of people and even of generations.

This is also the common field of veterinarians and medical doctors for formation and care of experimental animal models produced for treatment and diagnosis experiments of diseases in human beings. Medicines tried for human beings in the first place can be used for also the animals having similar diseases; and the reverse way can also be valid.

CONCLUSION

CMD are the common problems of all multicellular organisms. Collaborating for overcoming the problem will give great acceleration both to veterinary and medical world in terms of developments.

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