Published in final edited form as:

Vet J. 2007 September ; 174(2): 252–259. doi:10.1016/j.tvjl.2006.08.017.

Inherited metabolic disease in companion animals: Searching for nature's mistakes

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Abstract

Inborn errors of metabolism are caused by genetic defects in intermediary metabolic pathways. Although long considered to be the domain of human paediatric medicine, they are also recognised with increasing frequency in companion animals. The diagnosis of diseased animals can be achieved by searching for abnormal metabolites in body fluids, although such screening programmes have, until now, not been widely available to the small animal clinician. A comprehensive battery of analytical tools exists for screening for inborn metabolic diseases in humans which can be applied to animals and serve not only for the diagnosis of affected patients but also to detect asymptomatic carriers and further our understanding of metabolic pathways in dogs and cats. Moreover, naturally occurring animal models of inherited metabolic diseases provide a unique opportunity to study the biochemical and molecular pathogenesis of these disorders and to investigate possible therapeutic options.

Keywords

Inborn errors of metabolism; Companion animals; Inherited diseases; Metabolism; Diagnostic testing

1. Introduction

Inherited metabolic diseases, also termed inborn errors of metabolism (IEM), were first recognised at the beginning of the last century by Sir Archibald Garrod (Garrod, 1902) who recognised the association between Mendelian inheritance, phenotypic variation, and biochemical changes in metabolism. He initially studied alkaptonuria, an inherited defect of tyrosine metabolism where affected individuals excrete large quantities of homogentisic acid and develop joint problems, a disease not yet recognised in animals. Based upon the dark colour of the urine, Garrod observed that an individual is either alkaptonuric or normal and that this clinical manifestation persisted in a patient although the degree could be changed by diet. According to the familial distribution, he interpreted alkaptonuria as an autosomal recessive Mendelian trait. Alkaptonuria and the other metabolic disorders of which Garrod was then aware (cystinuria, porphyria, and pentosuria) occurred rarely in the population. At that time, and indeed until very recently, such conditions have been regarded as little more than curiosities. In fact, it took more than 50 years after Garrod's observation to characterise

the enzymatic block in alkaptonuria (La Du et al., 1958) and almost a further 40 years to unravel the molecular genetic defect of that disease (Fernandez-Canon et al., 1996).

Although Garrod had no idea of the existence of genes, he gave birth to the idea of 'IEM' whereby the lack of an enzyme (or a change in its function) leads to a 'block' in the metabolic pathway with accumulation of substrates before and lack of product formation after the 'block'. Based upon Garrod's ideas and the scientific advances over the past decades, an ever-increasing number of IEM are being detected and characterised (Scriver et al., 2001), from the clinical signs to the molecular level (>5,000 as of February, 2006 in the Online Mendelian Inheritance in Man (OMIM) website (www.ncbi.nlm.nih.gov)).

Inherited metabolic diseases have always been a domain of paediatric medicine; however, an ever-increasing number of descriptions from the animal kingdom have made it quite clear that IEM should also be considered in veterinary patients. This was recognised by Patterson, Jezyk, and colleagues in Philadelphia 30 years ago and led to the establishment of the Metabolic Genetics Disease Laboratory at the University of Pennsylvania. To date, almost 1000 inherited diseases are known in dogs and cats (Online Mendelian Inheritance in Animals <http://omia.angis.org.au>; the Cambridge Inherited Disease in Dogs Database, <http://www.vet.cam.ac.uk/idid>) and the Philadelphia group alone has characterised more than 50 of these diseases. The presence of an IEM in veterinary patients is still considered rare, but because of the common practice of inbreeding, some IEM have reached a high frequency in some breeds.

It is beyond the scope of this article and not our intention to include all IEM occurring in companion animals. Many inherited haematological disorders have been elegantly characterised and described, and functional or DNA carrier testing is available for some including bleeding disorders, immunodeficiencies, and erythrocyte defects (Brooks, 1999; Giger, 2000). This article focuses primarily on those inherited diseases resulting from defects in the catabolism of proteins and complex carbohydrates representing classical examples of IEM; however, mention is also made of other disorders resulting from defects in the transport of intermediary metabolites. On the basis of relatively discrete clinical signs and simple metabolite analyses, a differential diagnosis list can be made and further enzyme and molecular evaluation can lead to a definitive specific diagnosis.

2. Clinical presentation: when to consider an IEM?

Experience has shown that the path to diagnosis of an IEM can be tortuous and complicated. Disease heterogeneity and similarities to acquired disorders have shown that a diagnosis cannot usually be made based upon clinical signs alone as other factors, such as nutrition, infection, and growth, influence many metabolic pathways. However, some have very specific well-recognised clinical syndromes.

Are the clinical signs of an IEM in dogs and cats similar to those of affected children? Based upon the reported examples, it may well be safe to assume that they should be; however, many are relatively non-specific in children and animals (generalised weakness, growth retardation, weight loss or lack of weight gain, vomiting, lethargy, seizures, dyspnoea, skin abnormalities (hair loss), skeletal malformations, corneal clouding and other ocular changes). For example, the classical life-threatening clinical presentation of acute metabolic disease in neonates and young children (coma, metabolic acidosis, ketosis, encephalopathy, liver failure) may appear in affected animals, but many may die before a definitive diagnosis is made. Such signs may be part of the puppy/kitten mortality complex. The onset of clinical signs usually occurs early in life although some, such as some inherited eye diseases, mucopolysaccharidosis type III, and Fanconi syndrome, do not appear until adulthood. A common presenting sign is failure-to-thrive as affected animals lag behind healthy litter-

mates in their development and they do not gain weight at a normal rate. Signs of metabolic (organic) acidosis (lethargy, coma, vomiting, anorexia) are likely to occur, but may not be recognised as such. Nevertheless, there have been occasional reports of 'classical' organic acidurias (lactic aciduria and methylmalonic aciduria) in dogs with predominantly neurological signs (Podell et al., 1996). Isolated methylmalonic aciduria is characteristic of vitamin B12 malabsorption (Fyfe et al., 1991) in which patients present with a triad of failure-to-thrive, lethargy, and anorexia. If untreated, patients develop neurological signs of tremor, anxiety, and convulsions.

The concept of substrate accumulation due to a metabolic block in an intermediary pathway has led to the idea of metabolic intoxication (Fig. 1). This may be a double-edged sword. On the one hand there is a pathological effect caused by accumulated substrate prior to the 'block'. The accumulation of such toxic metabolites (e.g. CoA esters, organic acids) can lead to a wide variety of clinical signs. Secondary pathways are then activated to conserve CoA (e.g. carnitine or glycine conjugation) and increased levels of these secondary metabolites can be of diagnostic significance. On the other hand, the lack of product formation may lead to decreased energy production. The lack of product formation 'post block' severely limits the effectiveness of some catabolic pathways. Products are then unavailable for recycling or for further degradation. The main end-product of catabolism is energy in the form of ATP and any decrease in ATP production will inevitably lead to a state of energy deficiency. The signs of energy deficiency are highly varied and non-specific, but usually include hypotonia, growth retardation, and generalised weakness. A decrease in substrate oxidation can lead to an increase in lactate (lactic acidosis). In addition to musculoskeletal weakness, there is often multisystem involvement including the central nervous system (CNS), cardiovascular system, kidneys, liver, pancreas, and bone marrow. Histological investigations of skeletal muscle may reveal characteristic myopathic features such as ragged red fibres and a few metabolic studies have confirmed a mitochondrial defect (Table 1) (Shelton, 1999). Apart from the biochemical demonstration of pyruvate dehydrogenase deficiency in Sussex spaniels (Houlton and Herrtage, 1980) and an investigation in Old English sheepdogs (Breitschwerdt et al., 1992; Vijayasarathy et al., 1994), the direct determination of respiratory chain enzyme complex defects in skeletal muscle from dogs remains a major challenge.

Perhaps the best characterised IEM in dogs and cats are the lysosomal storage disorders. Defects in the intralysosomal degradation of large substrates produce an accumulation of partially degraded substrate that fills and expands the lysosome. This, in turn, leads to intracellular storage with organomegaly, corneal clouding, skeletal abnormalities with stunted growth, and neurodegenerative features (leukodystrophy, spasticity, visual impairment, ataxia, and seizures). Other organ systems such as cardiovascular and renal can also be affected. Abnormal epiphyses (dysostosis multiplex), when they occur, are usually quite characteristic for mucopolysaccharide (glycosaminoglycan) storage diseases. There are many naturally occurring lysosomal storage disorders in animals possibly due to the fact that they exhibit similar clinical features as affected humans and are not lethal early in life. Dogs and cats presenting with skeletal abnormalities, growth retardation, organomegaly, and visual impairment can be easily recognised. Dogs and cats with various forms of mucopolysaccharidosis (MPS), cats with alpha-mannosidosis and mucopolipidosis II, and dogs with alpha-fucosidosis and globoid cell leukodystrophy have been described (Table 1). Highly suggestive for a storage disorder is the presence of storage vacuoles or granules in white blood cells on a blood smear or a positive urinary MPS spot test result, but a specific metabolic, enzymatic, or molecular evaluation is needed to document the definitive diagnosis.

There are also several IEM suspected based upon secondary clinical features such as bladder calculi. For example, cystinuria in Newfoundlands (Casal et al., 1995) causes bladder and renal cystine calculi with a characteristic urinary basic amino-acid excretion pattern. This disease has now been defined in Newfoundland and Labrador retrievers at the molecular level (Henthorn et al., 2000; Henthorn and Giger, 2006). Cystinuria has also been described in other breeds including the Bassett hound, dachshund and mastiffs. Renal or bladder stones also occur in oxaluria in both cats (Blakemore et al., 1988) and dogs (Danpure et al., 1991) and xanthine stone formation due to hereditary xanthinuria has been observed in both dogs (Kucera et al., 1997) and cats (A.C. Sewell, personal observation; White et al., 1997). Renal uric acid stone formation without hyperuricaemia is a well-known trait in Dalmatian coach hounds (Schaible, 1986) and recent evidence has suggested that an unknown 'hepatic hormone' may influence the tubular reabsorption of urate in affected dogs (Simkin, 2005). Occasionally 'silent' IEM may be detected by chance as was the case in an Afghan hound with D+ glyceric aciduria (Sewell et al., 1997) or isovaleric aciduria in Siamese cats, both rare IEM with no apparent clinical sequelae.

3. Diagnostic procedures

Inborn errors of intermediary metabolism can occur in all metabolic pathways, most commonly the degradative pathways of amino-acids, fatty acids, carbohydrates (e.g. glycogen), glycoconjugates (glycosaminoglycans and glycoproteins), and purines/pyrimidines (e.g. uric acid). Making a tentative diagnosis is reliant on a combination of clinical signs (usually scant and non-specific) and a battery of laboratory investigations in body fluids. Table 2 gives a list of specialised laboratory investigations used for the diagnosis of IEM. Apart from the Metabolic Genetic Disease Laboratory at the University of Pennsylvania in Philadelphia (<http://w3.vet.upenn.edu/penngen>), which has offered a metabolic screening programme for dogs and cats for nearly three decades, most metabolic laboratories usually reside in human paediatric centres (as in the University Children's Hospital in Frankfurt, Germany). Such centres may be able to offer such a service; however, the necessary veterinary reference ranges for many metabolites may not be available and based upon standard operating procedures, these laboratories may not be permitted to handle animal material.

The interpretation of laboratory results requires some knowledge of 'normal' small animal metabolism. For example, dogs and cats are not prone to exercise-induced ketonuria which would complicate the diagnosis of inherited defects in mitochondrial fatty acid oxidation (assuming that they occur in companion animals) using urinary ketone body excretion as a marker. Likewise, hyperammonaemia, as a marker of deranged urea synthesis, may occur in cats secondary to a lack of dietary arginine (Giger and Haskins, 1994). Thus, it is most important to consider secondary causes of abnormal metabolite levels, particularly those of nutritional origin.

Imaging techniques can also be helpful to diagnosis. Skeletal radiographs to confirm clinical signs of several lysosomal storage disorders are important. Likewise, cranial magnetic resonance imaging (MRI) can reveal a leukodystrophy as in the diagnosis of L-2-hydroxyglutaric aciduria in Staffordshire Bull terriers (Abramson et al., 2003) and globoid cell leukodystrophy in West Highland white terriers and Cairn terriers (Cozzi et al., 1998; McGowan et al., 2000). Ophthalmological investigations are also helpful in detecting corneal clouding in patients with mucopolysaccharidosis, cataracts, and lens dislocation.

Examining urine by paper chromatography and a glycosaminoglycan spot test is a first screening approach to detect abnormal metabolites. Once screening identifies an abnormal compound, analysis of organic acids by gas chromatography/mass spectrometry, quantitative

amino acid analysis, and determination of glycosaminoglycans, oligosaccharides, purines, and pyrimidines can be performed for urine, serum, and cerebrospinal fluid. Most technologies require little sample volume (Giger and Jezyk, 1992; Jezyk et al., 1982).

The following two examples are given to illustrate the diagnostic potential of metabolite analysis. The first case, a six month-old pure-bred male Beagle was referred because of failure to thrive, lethargy, vomiting, and diarrhoea. Routine haematology revealed mild anaemia with an increased mean corpuscular volume and neutropenia. Serum bile acid concentrations were normal. A portosystemic shunt was considered, but ruled out by portal angiography. An ammonia tolerance test was abnormal. Urinary organic acid analysis revealed a dramatically increased methylmalonic acid excretion (17,091 mmol/mol creatinine; normal = <20 mmol/mol) with a trace of methylcitrate but no lactic acid. This result is indicative of cobalamin malabsorption syndrome and serum cobalamin levels were decreased. As previously reported by Fordyce et al. (2000), this patient was successfully treated by parenteral vitamin B12 administration every 2–4 weeks. Cobalamin malabsorption has also been described in giant Schnauzers (Fyfe et al., 1991), Border collies (Battersby et al., 2005), and Australian shepherd dogs (He et al., 2005). Investigations of affected Giant schnauzers and Australian shepherd dogs at the molecular level (Fyfe et al., 2004; He et al., 2005) have confirmed that this disease is a true homologue of congenital megaloblastic anaemia due to vitamin B12 deficiency because of a defect in the vitamin B12/intrinsic factor receptor (Imerslund-Gräsbeck syndrome) in humans. This disease is caused by mutations in either the gene encoding cubilin (Aminoff et al., 1999) or amnionless (Tanner et al., 2003).

The second case, a female domestic European short-haired cat, presented at eight months of age with generalised apathy, stunted growth, a hopping gait, and corneal opacities. The face was broad with a saddle nose and small ears. A radiographic survey showed generalised cardiomegaly, hepatomegaly, radiolucent vertebrae, broad ribs, and a deformed thoracic cavity. Examination of a peripheral blood smear revealed neutrophils with prominent cytoplasmic basophilic granules and vacuolated lymphocytes. The clinical signs and together with urinary glycosaminoglycan analysis demonstrating increased dermatan sulphate and chondroitin sulphate, suggested a lysosomal storage disorder. Assay of several lysosomal enzyme activities revealed one, β -glucuronidase, in the patient's plasma to have no activity when compared with plasma from normal cats, documenting the diagnosis of MPS VII (β -glucuronidase deficiency), which has also been found in domestic short-haired cats (Fyfe et al., 1999; Gitzelmann et al., 1994; Schultheiss et al., 2000) and German shepherd dogs (Haskins et al., 1984; Silverstein-Dombrowski et al., 2004).

The suspected diagnosis of IEM requires confirmation. This is usually in the form of enzyme analysis in serum/ plasma, leucocytes, cultured skin fibroblasts, or liver biopsy. For most lysosomal storage disorders, the respective enzyme assays are available for companion animals with the relevant reference ranges; however, for many other IEM, the necessary enzymatic confirmation is not available. In addition, the determination of enzyme activity usually does not provide a clear distinction between healthy individuals that are homozygous normal and obligate heterozygous, which for breeders is of utmost importance.

IEM in humans are generally caused by many different mutations in a particular gene, whereas in dogs and cats, the same mutation is typically responsible for a specific disease in a particular breed. Recently, great advances have been made in canine molecular genetics (Ostrander et al., 2000, 2006). Recombinant DNA technology has provided the means of detecting a genetic defect at the molecular level using the polymerase chain reaction (PCR) and can differentiate between genetically normal, carrier, and affected individuals. These can be performed at any age regardless of the onset of the disorder, requiring only a small

amount of blood (EDTA) or buccal swab (Giger et al., 2006). At present, mutations have been recognised in a total of 40 disorders of dogs and cats, and a dozen disorders have been fully characterised at the molecular level. As in human paediatric medicine, a well-documented case history is indispensable. In the case of dogs and cats, the determination of the pedigree and the occurrence of affected animals within the pedigree will provide valuable information on the mode of inheritance.

4. Conclusion

The provisional diagnosis of IEM may be based on breed, specific clinical findings, and routine screening tests. The analysis of metabolites in certain pathways may suggest a particular defect which can be confirmed by specific protein and molecular assays. The metabolic pathways of dogs and cats are, broadly speaking, identical to those in humans, and the same IEM can be expected to occur in most mammals. This has been proven by an ever-increasing number of IEM reported in dogs and cats.

At present, metabolite analysis in veterinary patients is limited to 'conventional' metabolites, i.e. amino-acids, organic acids, and mucopolysaccharides. In paediatric medicine, the search for an IEM is made easier because of the large arsenal of available laboratory tests. Adapting these tests for veterinary use is a challenge. Luckily, most of these tests require little sample volume; however, the 'behaviour' of veterinary material in our 'paediatric' systems is mostly unknown. For example, in paediatric inherited disorders of glycosylation, transferrin molecules have an altered electrophoretic mobility compared to healthy controls. When adapting this method for veterinary use, a completely different pattern for healthy canines was observed requiring an almost complete reworking of the protocol, a problem that today has not yet been completely solved (A.C. Sewell, unpublished data). New technologies, in particular tandem mass spectrometry, can be developed for veterinary use as this technique would enable the simultaneous detection of many metabolites in small samples of dried blood. Likewise, the analysis of neurotransmitters in CSF (a relatively new field in paediatric medicine) would be helpful in veterinary diagnostics for the relatively large numbers of companion animals that present with neurological signs. With the publication of the canine genome, the avenue of proteomics has been opened. As in human disease, proteomics can be divided into three main areas (structural protein analysis, expression, and functional analysis). For veterinary use, the analytical machinery will be available; however, the number of institutions willing to undertake such a task is extremely limited. In addition, the introduction of systems such as multiplex protein arrays, cytokine arrays, and tissue microarrays is at present purely theoretical due to limited antibody availability and prohibitive costs.

Beyond individual patient diagnosis and management, finding animal models of human genetic disease plays a role in human and animal health (Patterson et al., 1988). In the field of lysosomal storage disorders, animal models are well-known (Haskins et al., 2002). These animals have a similar clinical presentation and pathogenesis as the human diseases. The discovery of naturally occurring models of lysosomal storage diseases has enabled the development and assessment of efficacy and safety of enzyme replacement therapy and gene therapy approaches (Auclair et al., 2003; Casal and Haskins, 2005; Ellinwood et al., 2006; Crawley et al., 1996; Ponder et al., 2002). This has paved the way for therapy of the human disease.

Finding spontaneous mouse models, as well as producing knockout mice with a disruption of the gene of interest, provides the ability to evaluate disease and therapy on a relatively large number of animals with a uniform genetic background. However, domestic animals with spontaneous genetic disease can be of great importance in understanding pathogenesis

and the development of therapy. Veterinary medicine provides an increasingly high degree of medical scrutiny of animals, particularly the dog and cat, and new orthologues of human genetic diseases are being recognised with increasing frequency. These models provide an opportunity to monitor therapeutic efficacy and the possible development of untoward side-effects in out-bred, long-lived animals that can be monitored as individuals using the same methods that are applicable to human patients. To find such animals, metabolite analysis in body fluids of dogs and cats with clinical signs of disease is the first step in the search for large animal models of IEM; however, this first step depends on the clinical acumen of the primary veterinarian and, therefore, education in veterinary colleges and continuing education programs is required. The recognition of, and research into, inherited metabolic disease in companion animals will undoubtedly bring benefit to both human and veterinary patients alike.

Acknowledgments

The discovery and characterization of inborn errors of metabolism in dogs and cats is supported by a grant from the National Institutes of Health, RR02512.

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Fig. 1.

Schematic representation of the effect of an inherited enzyme defect in intermediary metabolism. The accumulation of toxic metabolites (organic acids) and a decreased substrate for biosynthetic pathways give rise to clinical signs and energy deficiency.

Table 1

Examples of inherited neurodegenerative disease in companion animals

	Breed	Reference
<i>Mitochondriopathy</i>		
	Jack Russell Terrier	Olby et al. (1997); Gruber et al. (2002)
	Clumber Spaniel	Jarvinen and Sankari (1996)
	Old English Sheepdog	Breitschwerdt et al. (1992); Vijayasarathy et al. (1994)
	Alaskan Husky	Brenner et al. (2000)
	Irish Terrier	Wentnik et al. (1974)
	Sussex Spaniel	Houlton and Herrtage (1980)
	German Shepherd dog	Paciello et al. (2003)
<i>Mucopolysaccharidosis</i>		
I	Cat	Haskins et al. (1979)
	Plott Hound	Shull et al. (1982)
II	Retriever dog	Wilkerson et al. (1998)
IIIA	Dachshund	Fischer et al. (1998)
	Huntaway dog	Jolly et al. (2000)
IIIB	Schipperke dog	Ellinwood et al. (2003)
VI	Siamese cat	Jezyk et al. (1982)
	Miniature Pinscher dog	Neer et al. (1995)
	Miniature Schnauzer dog	Berman et al. (2004)
	Chesapeake Bay Retriever dog	Haskins et al. (2002)
VII	German Shepherd dog	Silverstein-Dombrowski et al. (2004)
	Mixed breed dog	Haskins et al. (1984)
	Cat	Gitzelmann et al. (1994); Fyfe et al. (1999); Schultheiss et al. (2000); A.C. Sewell et al. (unpublished data)
<i>Glycoproteinoses</i>		
Alpha-Mannosidosis	Cat	Maenhout et al. (1988)
Alpha-Fucosidosis	Springer Spaniel dog	Healy et al. (1984); Skelly et al. (1996)
<i>Neurolipidoses</i>		
Mucopolipidosis type II	Cat	Mazrier et al. (2003)
GM1-Gangliosidosis	Alaskan Husky dog	Müller et al. (2001)
	Korat cat	De Maria et al. (1998)
	Siamese cat	Baker Jnr et al. (1971)
GM2-Gangliosidosis Type Sandhoff	Retriever dog	Yamato et al. (2002)
	Shorthaired cat	Yamato et al. (2004)
Krabbe disease (galactocerebrosidase deficiency)	Cairn Terrier and West Highland White Terrier dog	Wenger et al. (1999)
	Longhaired cat	Sigurdson et al. (2002)
<i>Other</i>		
L-2-Hydroxyglutaric aciduria	Staffordshire Bull Terrier dog	Abramson et al. (2003)
	West Highland White Terrier dog	Garosi et al. (2005)

Table 2**Metabolite analyses for detecting IOM**

Urine	Amino acids, organic acids, oligosaccharides, glycosaminoglycans, purines/pyrimidines, orotic acid, uric acid, monosaccharides
Serum/plasma	Blood gases, electrolytes, uric acid, lactate, glucose, pyruvate, ammonia, copper, caeruloplasmin, amino acids, organic acids, very long-chain fatty acids, phytanic acid, biotinidase, enzyme activities
CSF	Protein, glucose, lactate, amino acids, organic acids, neurotransmitters
Whole blood	Leukocyte preparation for enzyme assay, EDTA blood for molecular analyses
Tissue	Liver biopsy (histology), skin biopsy (histology/fibroblast culture), muscle biopsy (histology)