BIOCONTROL
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Specialist information

Inborn errors of metabolism

In dogs and cats

Screening for Inborn errors of metabolism

Key Facts

- **Screening tests of blood and urine allow the diagnosis of inborn errors of metabolism**
- **Clinical signs are caused by enzyme defects leading to the accumulation of metabolic products or insufficient product formation**
- **The ingestion of chicken jerky treats has been linked to acquired Fanconi syndrome**

Introduction

Inborn errors of metabolism (IEM) are an important group of diseases in both cats and dogs and are associated with a wide range of mostly unspecific clinical signs. Sir Archibald Garrod was the first to recognise a link between phenotypic characteristics according to Mendelian genetics and biochemical alterations in metabolism [1].

He concluded that the pattern of inheritance of certain IEM is autosomal recessive and suggested that the cause is an altered or lacking enzyme activity in a specific metabolic pathway.

Such enzyme defects lead to an accumulation of substrates prior to the metabolic block, altered/abnormal metabolic products or insufficient product formation [2]. These can in turn cause clinical signs and symptoms.

IEM can be classified based upon various criteria.

Simple screening tests for aminoacids, organic acids and complex carbohydrates (mucopolysaccharides and oligosaccharides) provide the initial suspected diagnosis of an IEM; further specific tests are required to confirm the diagnosis [3].

inborn errors of metabolism	
according to subcellular localisation	e.g. ■ lysosomal ■ mitochondrial ■ peroxisomal
according to histology or imaging	e.g. ■ eukodystrophy ■ systemic atrophy
according to affected metabolites and enzymes	e.g. ■ copper
according to affected functional pathways	e.g. ■ glycolysis ■ citric acid cycle ■ urea cycle ■ respiratory chain

TAB. 1 Classification of Inborn errors of metabolism

Aminoacids

The analysis of aminoacids in plasma and urine is part of screening for IEM.

Aminoacids are necessary for protein synthesis and are provided either by nutrition or by cellular synthesis. Together with the so-called ‚non-essential' amino-acids, i.e. those that are produced by the body, the 'essential' aminoacids (arginine, histidine, leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine) have an absolute requirement and can only be obtained via external nutrition.

When do I order aminoacid analysis?

1. Suspected taurine deficiency

The sulphur-containing aminoacid taurine is essential for cardiovascular function and the development of skeletal muscle, the retina and the central nervous system. Compared to dogs, cats have a dietary requirement for taurine as they cannot synthesis it; there-fore cat foods contain supplementary taurine.

In dogs, a nutritionally related taurine deficiency can lead to dilated cardiomyopathy [4]. I

n this case, assay of taurine in frozen EDTA-plasma is required.

2. Suspected cystinuria (COLA-Test)

Cystinuria is an IEM caused by a defective transport of specific aminoacids (cystine, ornithine, lysine and arginine = COLA) in intestinal epithelium and the proximal renal tubule. The disease is known to occur in more than 70 breeds of dog including Newfoundler, Mastiff, Bassett Hound and Irish Terrier. The defective transporter leads to a failure to reabsorb COLA with a subsequent increased renal excretion of these amino-acids. Cystine is highly insoluble in urine at acidic pH and forms crystals and calculi with severe clinical symptoms [5].

Analysis of aminoacids (COLA) in random urine (10 ml frozen) is necessary to provide the diagnosis. A COLA level >500 µmol/g creatinine is indicative of cystinuria [6].

3. Suspected renal Fanconi syndrome

Debré-de-Toni-Fanconi syndrome is an IEM caused by a loss of energy in the cells of the proximal renal tubule leading to a failure to reabsorb a variety of metabolites.

Glucose, phosphate, aminoacids and carnitine are not resorbed and appear in increased concentrations in the urine. Affected patients exhibit glucosuria and hyperaminoaciduria.

A breed-specific form of the disease has been characterised in Basenji dogs [6]) and there are reports of renal Fanconi syndrome caused by the ingestion of chicken jerky treats [7]. This has been observed mainly in the United States and Australia with sporadic cases reported in the UK and Austria. The disease affects mainly toy breeds and is reversible when recognised early.

The determination of aminoacids in random urine (10 ml frozen) is necessary to diagnose the hyperaminoaciduria characteristic of renal Fanconi syndrome.

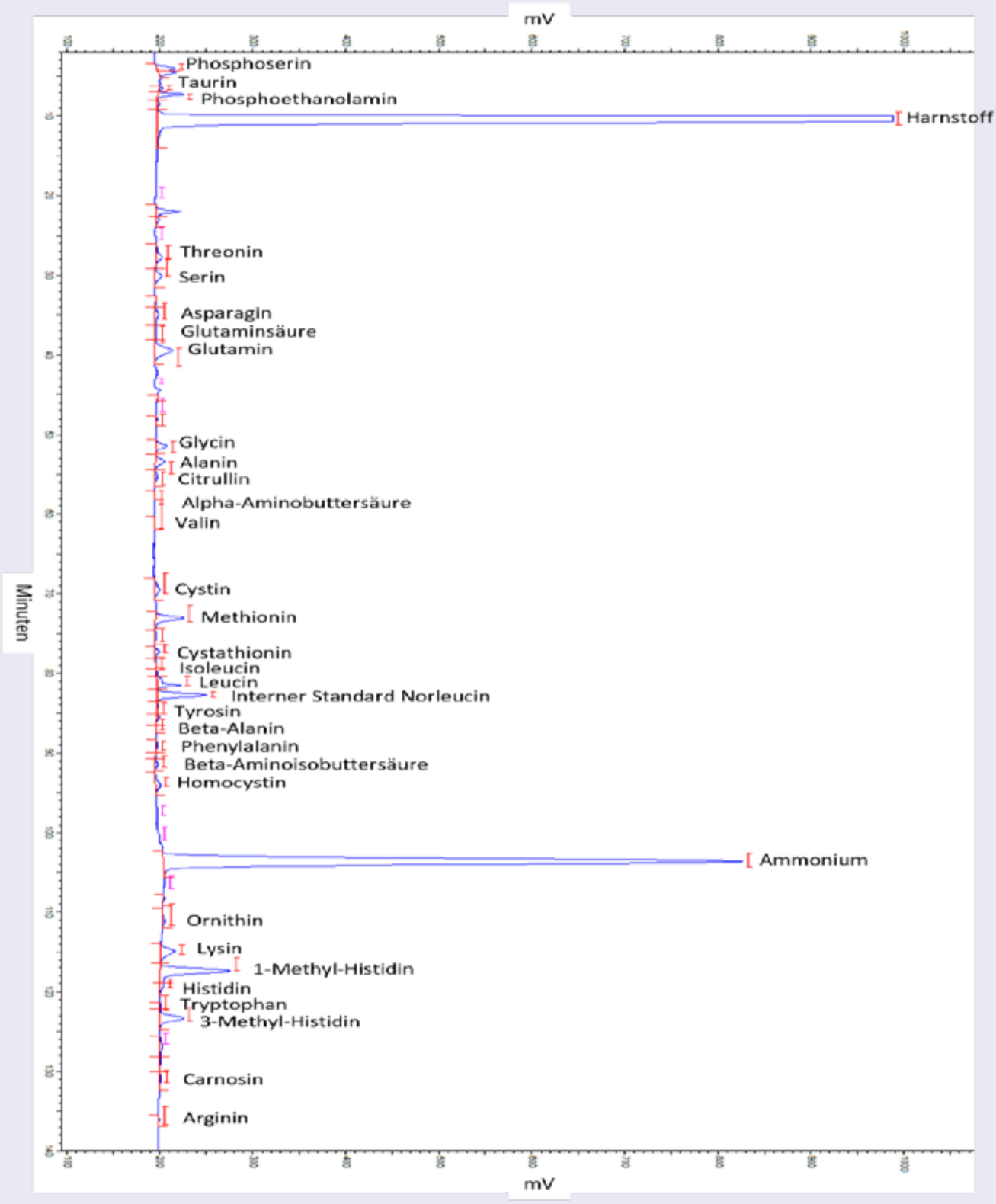

ABB. 1 Chromatogram of urinary aminoacids in normal urine.

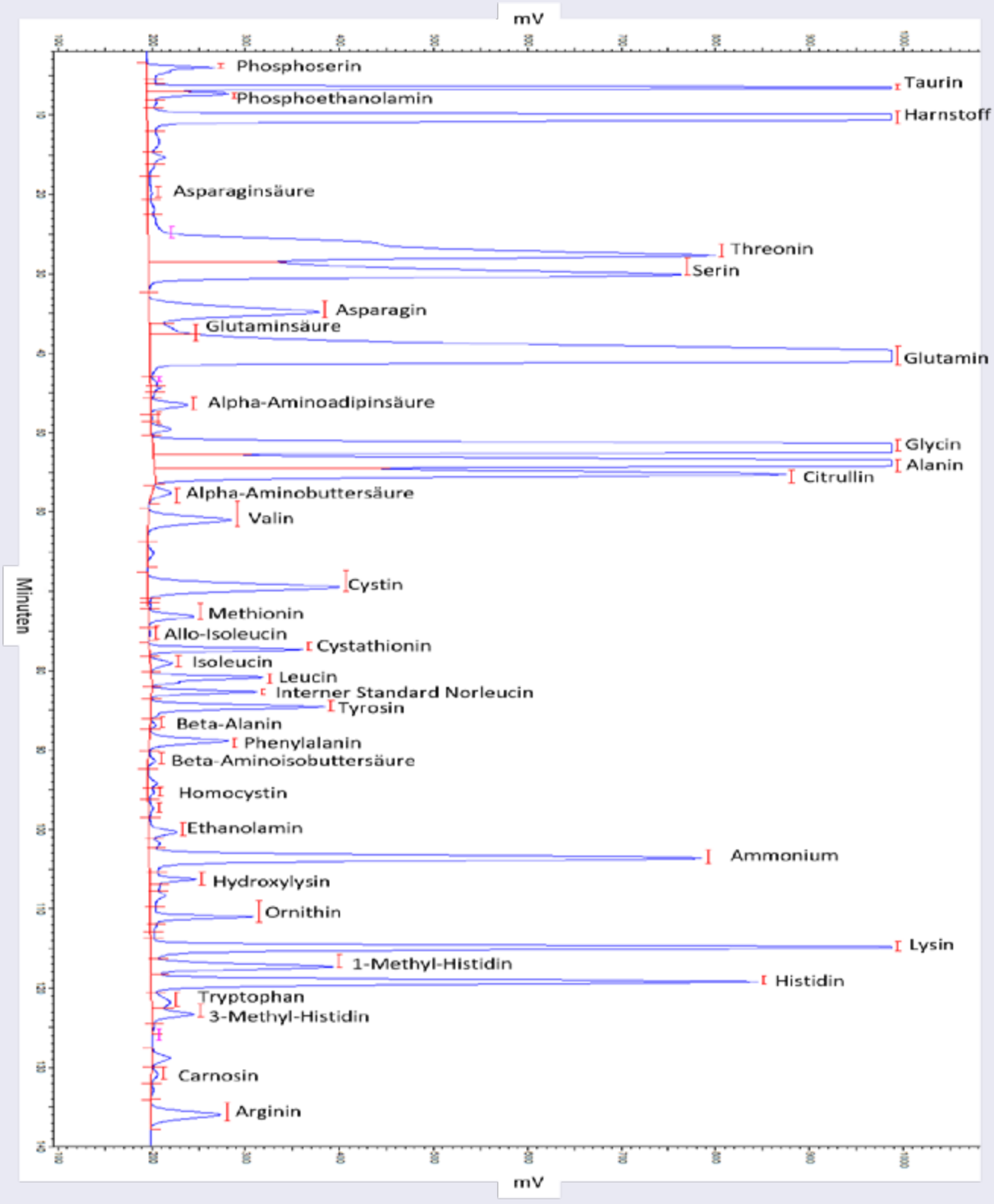

ABB. 2 Chromatogram of urinary aminoacids in a case of renal Fanconi syndrome. Note the severe hyperaminoaciduria.

Organic acids

The analysis of urinary organic acids, as with plasma aminoacids, is an important cornerstone in the diagnosis of IEM.

Organic acids are products of the intermediary metabolism of aminoacids, fatty acids and carbohydrates.

The lack of specific enzymes in complex catabolic pathways leads to an accumulation of organic acids and their increased excretion in urine.

When do I order an organic acid analysis test?

1. Suspected cobalamin (vitamin B12) malabsorption

Selective intestinal cobalamin (vitamin B12) malabsorption is an autosomal recessively inherited metabolic disease present with an increased incidence in Border Collies, Beagles, Giant Schnauzers, Shar Peis and Australian Shepherd dogs [8]. Affected patients have low serum cobalamin levels and an increased urinary excretion of methylmalonic acid.

So far DNA testing is only available for Beagles and Border Collies. In the other affected breeds testing urine for methylmalonic acid is necessary.

Methylmalonic acid is detected in the course of urinary organic acid screening (10 ml random urine) which, together with the assay of vitamin B12 in serum (1-2 ml), confirms the diagnosis.

If shipment is expected to take >24 h freeze both and ship frozen.

2. Neurodegenerative disorders

Progressive neurodegenerative signs (e.g. increased gait ataxia) in cats and dogs are an indication for urinary organic acid analysis.

This investigation usually aims at excluding a wide range of IEM but, however, can be instrumental in revealing L-2-hydroxyglutaric aciduria in Staffordshire Bull Terriers and West Highland White Terriers [9].

Requirement is 10 ml random urine. If shipment is expected to take >24 h freeze and ship frozen.

Lysosomal storage diseases

Lysosomal storage diseases are a group of IEM in which macromolecules (e.g. mucopolysaccharides and glycoproteins) cannot be catabolised due to an enzyme defect.

The undegraded substrates accumulate in cells and organs whose functions are disturbed and create the signs and symptoms of the disease. These diseases, although rare, have been extensively characterised in people. Several diseases also occur in cats and dogs, many are breed-specific and have also been well characterised, some at the molecular level [10, 11]

When do I need to order a Mukopolysaccharide and Oligosaccharide test?

Lysosomal storage diseases are hallmarked by progressive neuronal degeneration.

Initial clinical (cerebellar) signs include tremor, ataxia and dysmetria.

Further signs such as organomegaly (may be subtle), corneal clouding on opthalmological testing, skeletal abnormalities, hypo-hyperreflexia, spasticity and sometimes increased seizure activity suggest a lysosomal storage disease.

The testing of a random urine sample (10 ml or 3 ml, respectively) for increased mucopolysaccharidurie and abnormal oligosaccharides can lead to a diagnosis.

Should other inborn errors of metabolism be suspected please do not hesitate to contact us.

Literature

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Haftungsausschluss

Die Erkenntnisse der Tiermedizin unterliegen stetigem Wandel durch Forschung, Neuentwicklungen und klinische Erfahrungswerte.

Trotz sorgfältiger Prüfung und Recherche kann Biocontrol für Dosierungen und Applikationsformen von Medikamenten sowie für die Vollständigkeit der diskutierten Themengebiete keine Gewähr übernehmen.

Jede medizinische Fragestellung muss individuell für den jeweiligen Patienten betrachtet, jede weiterführende Diagnostik und jede Therapie auf das entsprechende Tier und dessen Bedürfnisse sowie die Anforderungen des Tierhalters zugeschnitten werden.

Die von uns angefertigten Labor-Informationen sind als unterstützender Leitfaden zu betrachten, ersetzen aber nicht die kritische Auseinandersetzung mit der Fachliteratur und ggf. die Konsultation von Spezialisten.

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