

INTRODUCTION

Inborn errors of metabolism are individually rare but as a group are numerous. Many physicians consider them too rare and should only be considered after common conditions (i.e. sepsis) have been excluded - this is not the case!

Most of these diseases cannot be detected by newborn screening for various reasons therefore **clinical acumen is extremely important**. It is well known that in the neonate presenting with severe metabolic acidosis or hyperammonaemia, an inborn error of metabolism must be excluded; however, we are confronted daily with patients who present with a wide range of symptoms and in whom an inborn error of metabolism may also be suspected.

It is quite impossible to provide here details of **all** metabolic diseases and methods of diagnosis, therefore only a brief summary is given.

There now follows a list of analyses and examples of diseases detected:

LACTATE IN SERUM, URINE AND CSF

The determination of lactate in patients with a metabolic acidosis provides information on primary or secondary lactic acidoses. Defects in energy metabolism (e.g. **mitochondriopathies**) usually present with a primary lactic acidosis. These patients require further diagnostic work-up (**alanine in plasma, lactate in CSF**) culminating in determination of **respiratory chain enzymes** in muscle biopsies.

AMINOACIDS IN PLASMA, URINE AND CSF

A quantitative aminoacid analysis will provide information on primary disturbances in aminoacid catabolism, provided the metabolic block is only one or two steps down the pathway. This means, for example, that **phenylketonuria, maple syrup urine disease** and **tyrosinaemia** can be diagnosed. Confirmatory

tests for phenylketonuria (**tetrahydrobiopterin loading**) to exclude cofactor deficiencies are mandatory.

Confirmation of other diseases requires urinary organic acid analysis. **Tyrosinaemia type 1** can be confirmed by qualitative analysis of **succinylacetone** in dried blood spots and urinary organic acids.

Determination of glycine in CSF is vital to confirm **non-ketotic hyperglycinaemia**.

In cases of **hyperammonaemia**, plasma aminoacid and urinary orotic acid analyses must be performed to diagnose a urea cycle defect.

Classical **homocystinuria (cystathione- β -synthase deficiency)** is not always detected by routine aminoacid analysis. High **methionine** levels may be indicative. Very low **methionine** levels (virtually undetectable) may indicate **methyltetrahydrofolate reductase deficiency**. In both instances, a special analysis for **homocysteine** is mandatory.

ORGANIC ACIDS IN URINE, SERUM AND CSF

Apart from presenting with 'classical' symptoms of metabolic acidosis e.g. **methylmalonic aciduria, HMG-CoA lyase deficiency** and **propionic aciduria**, many patients with an underlying organic aciduria show symptoms of neurological delay (e.g. **4-hydroxybutyric aciduria, Canavan disease, L-2-hydroxyglutaric aciduria**). Thus, a urinary organic acid analysis is an integral part of the diagnostic work-up. Further analyses in serum and CSF may be necessary to search for metabolites in cases with severe neurological signs (e.g. **glutaric aciduria type 1**). **Fatty acid oxidation defects** can be detected by a combination of urinary organic acid and **carnitine** analyses.

Acylcarnitine profiling by tandem mass spectrometry is nowadays necessary.

BIOTINIDASE IN SERUM

Patients with severe biotinidase deficiency might present in the newborn period with metabolic acidosis and dermatitis. If untreated, patients will be neurologically

compromised. As treatment consists of oral high-dose biotin and is very effective, all patients with developmental delay should be checked for biotinidase deficiency.

GUANIDINOACETATE IN URINE

Recently, patients have been diagnosed with defects in creatine synthesis. They exhibit primarily neurological deficits. These patients cannot synthesise creatine and creatinine and excrete **guanidinoacetate** in urine. Patients respond dramatically to creatine therapy.

Creatine synthesis defects should be considered in all patients with seizures and developmental delay.

VERY LONG CHAIN FATTY ACIDS IN SERUM/PLASMA

Determination of **very long chain fatty acids** and their ratios in plasma is the first step in diagnosing a **peroxisomal disorder**. Abnormal ratios require further differentiation to provide a diagnosis, i.e. **adrenoleukodystrophy** or **Zellweger syndrome** (clinical differentiation!). Increased phytanic acid will provide a diagnosis of **Refsum disease** or **rhizomelic chondrodysplasia punctata**. Further diagnostic steps involve plasmalogen analysis and finally genotyping.

MUCOPOLYSACCHARIDES AND OLIGOSACCHARIDES IN URINE

Diagnosis of **lysosomal storage diseases** (e.g. **mucopolysaccharidoses types I Hurler, II Hunter etc., mannosidosis, sialidosis, GM1-gangliosidosis**) relies primarily upon the demonstration of increased abnormal urinary **mucopolysaccharides (glycosaminoglycans)** and **oligosaccharides** based on clinical suspicion (i.e. dysmorphic features, skeletal abnormalities etc.). As the clinical presentation of **sialic acid storage disease** is very similar, a urinary screen for excess **sialic acid (neuraminic acid)** should be performed. Confirmation can only be achieved by **specific enzyme analysis**.

Diagnosis of **metachromatic leukodystrophy** and other **glycolipid storage diseases** (e.g. **Fabry dis-**

ease, Krabbe disease) is only possible by **specific enzyme assay in leucocytes (white blood cells)**.

OTHER ANALYSES

The clinical presentation may be so unspecific that a wide variety of diagnostic tests is required. Occasionally, specific features may pinpoint a diagnostic avenue. The following tests may go some way towards narrowing the field:

1. **CDT and isoelectric focussing of transferrins** to diagnose congenital disorders of glycosylation.
2. **Purine and pyrimidine analysis** for **Lesch-Nyhan disease, xanthinuria, dihydro-pyrimidine dehydrogenase deficiency**.
3. **Porphyryn analysis** for **congenital porphyria**.
4. **Bile acids** for **congenital disorders of cholestasis** (not routinely available!).
5. **Copper and ceruloplasmin** for **Menkes disease and Wilson disease**.
6. **Oxalic acid and citrate** in urine for **primary and secondary oxaloses**.
7. **Neurotransmitter analysis** in CSF in cases of **BH4-responsive hyperphenylalaninaemia** (upon special request only!).
8. **Specific hormones** and urinary **pregnanes**.

Selective screening for inborn errors of metabolism requires a multidisciplinary approach. The clinical symptoms may well give an indication in which direction to search; however, a broad range of laboratory tests is usually necessary. Interpretation of such specialised metabolic investigations relies upon appropriate clinical data and experience. Information

on medication and nutritional status is required to avoid possible diagnostic errors.

Bioscientia is committed to providing as complete a programme as possible for the diagnosis of your patients with suspected metabolic disease.

An experienced team is on hand to answer any queries you may have related to diagnosis and treatment of inborn errors of metabolism. Please contact us if you are interested in any of the analyses listed here.

For sample requirements please refer to the current test list.

Author: Dr. Adrian C. Sewell, Director, Metabolic Laboratory
University Children's Hospital, Frankfurt am Main, Germany
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CONTACT/ADDRESS

BIOSCIENTIA
INT. SUPPORT SERVICES DEPT.
KONRAD-ADENAUER-STR. 17
55218 INGELHEIM
GERMANY
Phone: ++49-6132-781-203, 224 or 165
Fax: ++49-6132-781-236
E-mail: int.support@bioscientia.de
Website: www.bioscientia.de

BIOSCIENTIA REGIONAL HEADQUARTERS
MANAGER INT. MARKETING
MR. DAVID ISAAC
P.O. Box 3264
DUBAI
UNITED ARAB EMIRATES
Phone: ++971-4-397-4948
Fax: ++971-4-397-4129
E-mail: bioscien@emirates.net.ae
Website: www.bioscientia.de

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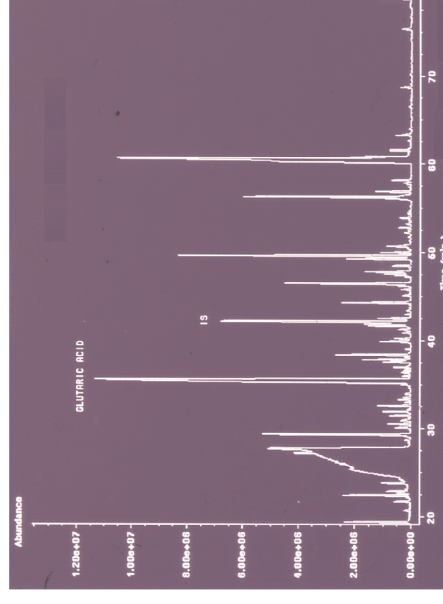
INSTITUTE FOR
LABORATORY
ANALYSES

Konrad-Adenauer-Str. 17
55218 Ingelheim, Germany

Phone: ++49-6132-781-203, 224 or 165
Fax: ++49-6132-781-236

E-mail: int.support@bioscientia.de
Website: www.bioscientia.de

SELECTIVE SCREENING FOR INBORN ERRORS OF METABOLISM



Urinary organic acids in a patient with glutaric aciduria type 1

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