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Newborn screening: Test list

Disorders of galactose metabolism

1. Galactose1-phosphate-uridyltransferase deficiency* (Gal.Gal-1P)
2. Galaktokinase deficiency* (Gal.Gal-1P)
3. UPD-glactose-4-epimerase deficiency* (Gal.Gal-1P)

Disorders of amino acid metabolism
(Tandem Mass Spectrometry/TMS: Aminoacids)

4. Phenylketonuria/Hyperphenylalaninemias
5. Maple syrup urine disease (MSUD)
6. Citrullinemia
7. Argininosuccinic aciduria

Organic acidemias (TMS: acylcarnitines)

8. Propionic acidemia
9. Methylmalonic acidemia
10. Isovaleric acidemia
11. Glutaric acidemia type 1

Disorders of fatty acid oxidation
(TMS: acylcarnitines)

12. Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
13. Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
14. Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency/trifunctional protein (TFP) deficiency
15. Multiple-acyl-CoA dehydrogenase (MAD) deficiency

Disorders of carnitine metabolism
(TMS: acylcarnitines)

16. Carnitine transporter deficiency
20. Carnitine palmitoyl transferase I deficiency
21. Carnitine palmitoyl transferase II deficiency
22. Carnitine translocase deficiency

Single Tests

23. Hypothyroidism (ELISA, quantitative: TSH)
24. Congenital adrenal hyperplasia (ELISA, quantitative: 17-OH-Progesterone)
25. Biotinidase deficiency (enzyme activity)

* rare disorders which can only be detected if sufficient lactose has been ingested

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01.2008

Specimen requirement

How neonatal screening is achieved

The first step:
blood collection (specimen requirement)
Blood is collected by heel prick or venous puncture, taken between the 36th and 72nd hour of life. The laboratory needs 6-7 drops of blood on a special filter card, available from Bioscientia. Each spot has to be saturated with one big drop of blood. After drying the sample in ambient air without the application of any additional heat or light this material is suitable to be sent to us.

The second step:
providing the necessary information/patient data
The laboratory has to be informed of name and sex of the baby. To correctly interpret the analytical results the day and hour of birth and of blood collection as well as birth weight and gestational age must be quoted.

The third step:
sending the sample
It is very important that we receive the sample as quickly as possible to allow a prompt diagnosis for the immediate commencement of treatment before symptoms arise.

Accredited by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
ZLG-P-366.07.02

Bioscientia has been CAP accredited since 1987

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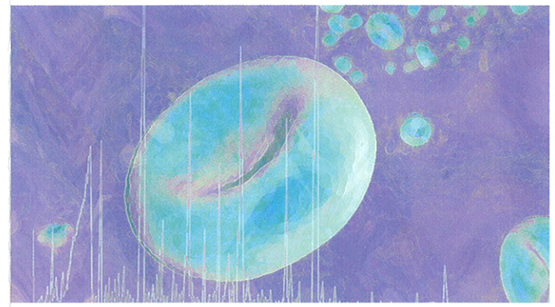

Newborn Screening for the early detection of inborn errors of metabolism

Test: Inborn errors of metabolism to detect

- Congenital hypothyroidism
- Congenital adrenal hyperplasia
- Aminoacidopathies
- Organic acidemias (or acidurias) including isovaleric acidemia and glutaric acidemia
- Disorders of fatty acid oxidation including medium-chain-acyl-CoA dehydrogenase (MCAD) deficiency
- Biotinidase deficiency
- Galactosemia

Congenital hypothyroidism

Congenital hypothyroidism occurs sporadically, with an incidence of one in about 4.000 newborns; some familial cases have been described. Dysgenesis or ectopic position of the thyroid gland are common causes of the disease. Treatment is achieved by giving the necessary dose of thyroxine.

Congenital adrenal hyperplasia

A defect in the biosynthesis of cortisol leads to hyperplasia of the adrenal glands, resulting in an overproduction of androgens and in a deficiency in mineralocorticoids. An acute salt wasting crisis which is lethal in many cases can result. Measurement of 17-Hydroxyprogesterone in term babies can detect this inborn error of steroid metabolism. Blood samples exceeding the cut off level of the immunoassay will be further analysed by tandem mass spectrometry to distinguish between true and false positive cases.

Aminoacidopathies

Disorders of amino acid metabolism are caused by inherited enzymatic defects in the relevant metabolic pathways. Phenylketonuria (PKU) is the most important one. Without early treatment it leads to severe mental retardation. During the first days and weeks of life these babies show no signs of disease. Diagnosis by clinical means alone is therefore insufficient. Citrullinemia is a rare disorder of the urea cycle, resulting from argininosuccinate synthetase deficiency. In some cases, it presents as an overwhelming disease on the first days of life. In some other cases late onset of symptoms is observed. Neonatal screening will allow early diagnosis and treatment to prevent metabolic crisis and severe neurological defects at least in late onset cases.
By measuring a spectrum of amnio acid concentrations in blood there is a chance to also detect very rare diseases like maple syrup urine disease.

Organic acidemias (or acidurias)

Organic acidemias present as acute or more chronic disorders, neonates presenting with seizures, metabolic acidosis or feeding problems and lethargy. The mainstay of longterm treatment consists of reduced intake of branched chain aminoacids which lead to production of organic acids. Although it is not possible to detect all known organic acidemias during the first days of life, there is a good chance to detect isovaleric acidemia and glutaric academia before clinical disease becomes obvious.

Disordeners of fatty acid oxidation

Generation of energy from fat is necessary in situations of high metabolic turnover or when other sources of energy are failing which happens in fasting periods or during infectious diseases.
The body uses fat mainly by stepwise degradation of long chain fatty acids to short chains via the so called β-oxidation pathway, located in mitochondria. A large number of enzymes are involved, many of which may show inherited functional defects thus causing specific diseases. Not all of them produce detectable biochemical abnormalities, but some can be discovered rather easily by tandem mass spectrometry during the first days of life. The incidence of disorders of ß-oxidation shows a great variability among populations and races. The defect of enzymatic degradation of medium chain fatty acids (MCAD-defect) however is the most important one. Although some of the children carrying this defect will never develop a clinical disease, others may die after acute metabolic decompensation. Therapy does not require any aggressive treatment. However, it is necessary to ensure sufficient carbohydrate intake at all times, especially at times of metabolic stress.

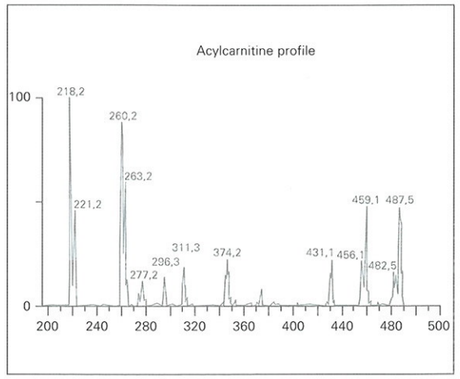

Fig. 1:
Tandem mass spectrometry: Acylcarnitines, normal pattern

Biotinidase deficiency

Biotin, also called Vitamin H, is the functional group of four important enzymes. If biotinidase is lacking sufficient activity the body loses biotin via urine in form of biocytine; in addition, not all of the biotin contained in food can be absorbed. The resulting disease, which can be prevented easily by oral application of free biotin, is called late onset multiple carboxylase deficiency. The incidence is rather low. However, clinical diagnosis is very difficult though treatment is easily achieved and prevents severe (neurological) symptoms. Therefore, many screening laboratories have added the test to their programs.

Galactosemia

Three different forms of galactosemia are known. The incidence is about one in 40.000 newborns. In galactokinase deficiency dietary treatment is preventing cataracts of the eye lens, however, classical galactosemia is more difficult to manage. Without diagnosis, affected children may die from liver failure. They can be saved by withholding lactose in the diet. For longterm prognosis however one has to keep in mind that some of the sequelae will develop irrespective of the quality of therapy.

Example report text for inborn errors of metabolism screen

Analyte or procedure	Results	Normal range	Unit
Visual Quality of blood card	good	–	
Thyroid stim. hormone (TSH)	unremarkable	<15	mU/ml
17-OH-Progesterone	unremarkable	<60	nmol/l
Galactose (GAL, GAL-1-P)	unremarkable	<30	mg/dl
Biotinidase	unremarkable	>30	% activity
Phenylalanine	unremarkable	<3.0	mg/dl
Spectrum and ratios of 7 amino acids	unremarkable	–	
Spectrum and ratios of acylcarnitines	unremarkable	–	

The analysis did not give any indication of
- Congenital hypothyroidism (TSH)
- Congenital adrenal hyperplasia (17-OH-progesterone)
- Galactosemia (GAL, GAL-1-P)
- profound biotinidase deficiency (Biotinidase)
- phenylketonuria, maple syrup urine disease or citrullinemia (amino acids: Phe, Tyr, Leu/Ileu, Val, Cit)
- propionic-, isovaleric-, methylmalonic- or glutaric acidemia, or MCAD deficiency (acylcarnitines: carnitine and 32 acylcarnitines, tandem mass spectrometry)

It is important to bear in mind that neonatal screening will not reveal inborn errors of metabolism or endocrinopathies when biological processes or therapy keep analytes in vivo in a normal range. An exact medical examination is mandatory if any symptoms of such diseases occur. The results are valid only when the infant was at least 36 hours old and has not received any blood transfusion prior to blood collection.Please note that the cut-off for 17-OH-progesterone depends on gestational age and/or birth weight.