

# **Selective screening for inborn errors of metabolism (IEM) in paediatric intensive care unit (ICU) patients**

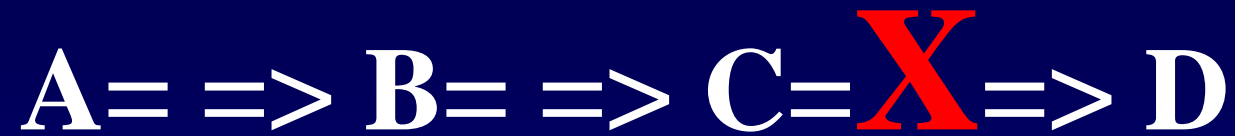
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Germany

# IEM

are caused by enzyme defects or coenzyme deficiencies disturbing metabolic pathways of

- amino acids
- organic acids
- fatty acids
- carbohydrates
- other compounds

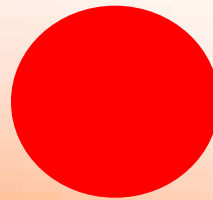
# Enzyme defects cause



**accumulation of metabolites**

# Conventional newborn screening

Guthrie card



PKU, MSUD, hypothyreosis,  
biotinidase deficiency,  
tyrosinemia

# Newborn screening by tandem mass spectrometry

- Aminoacidopathies
- Organic acidurias
- Fatty acid  $\beta$ -oxidation deficiencies.

**Selective screening:**

**Examination of patients**

**(pre-selected according to certain  
criteria)**

**for certain groups of disorders**

# The clinical picture of IEM

- The acute metabolic crisis of the newborn
- The chronic recurrent manifestation
- The neurodegenerative course of a disease

# The acute metabolic crisis of the newborn

- Poor feeding, loss of weight
- Recurrent vomiting, dehydration
- Muscular hypotonia
- Dyspnoea, apnoea
- Convulsions, apathy, somnolence, **coma**
- Hypoglycaemia
- Metabolic acidosis/ketoacidosis
- Lactic acidemia, hyperammonaemia.

# The chronic recurrent manifestation of an IEM

- Multiple episodes of severe vomiting
- Lots of acidotic, ketoacidotic, hypoglycaemic, hyperammonaemic attacks leading to
- Psychomotor retardation
- Epilepsia.

# The neurodegenerative type of an IEM

- **Ataxia**
- **Myoclonus**
- **Extrapyramidal disturbances**
- **Epilepsia**
- **Metabolic stroke**
- **Macrocephalus.**

# Example of an acute metabolic crisis in a newborn

- Neonatal death of two older siblings
- Normal pregnancy and delivery
- Vomiting after 24 hours of life
- Muscular hypotonia, lethargy, dyspnoea
- Development of **coma** and decompensated metabolic acidosis during the 2<sup>nd</sup> - 3<sup>rd</sup> day
- Death at the 6<sup>th</sup> day of life
- Selective screening: propionic acidemia.

# Propionic acidemia

Amino acids: Ile, Met, Thr, Val



↑↑↑ Propionyl-CoA ↑↑↑



**X**

PCC

Methylmalonyl-CoA

# **Example of the chronic manifestation of an IEM (1)**

- **Until 9 years of age - normal development**
- **Inappetence the evening before admission**
- **Next morning - somnolence, muscular hypotonia. Transfer to a hospital**
- **Hypoglycaemia (2,2 mmol/l) on admission, no meningitis or encephalitis**
- **Recovery under i. V. glucose.**

## **Example of the chronic manifestation of an IEM (2)**

- **At the age of 15 months - apathy**
- **Recovery after breakfast**
- **Diagnosis of a slight tympanitis.**

# **Example of the chronic manifestation of an IEM (3)**

- **At the age of 25 months - gastroenteritis, treated with “Imodium” (morphine deriv.)**
- **Vomiting. After 4 days the patient got soporous**
- **Admission to the hospital**
- **Successful treatment with i. V. glucose**
- **IEM suspected. Selective screening:**
- **Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency.**

# Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

- High frequency (1:6 500 - 1:17 000) in Caucasians
- Clinical onset between 3-24 months
- Acute metabolic decompensation with Reye-like syndrome and **coma** following prolonged fasting or intercurrent infection.
- Unexpected sudden death during the first decompensation is common.

# **Example of the neurodegenerative type of an IEM (1)**

- **Consanguinity of the Turkish parents**
- **Gravity, delivery, and the first few years of life were uneventful**
- **With 4 years, signs of slight developmental retardation**
- **Insufficient performance at school.**

# **Example of the neurodegenerative type of an IEM (2)**

- **With 9 years admission because of intension tremor and clear psychomotor retardation**
- **Leucodystrophic process (subcortical medulla, globus pallidum, nucleus dentatus)**
- **L-2-Hydroxyglutaric aciduria (enzyme defect unknown, no specific treatment).**

# An IEM has to be suspected

relying solely on

rather unspecific clinical  
signs

+

results of routine laboratory  
investigations

# Indications for selective screening

## Family history + anamnestic data

- **Consanguinity of the parents**
- **Certain diseases known in the family (neurol. disorders, maternal PKU, abortions, HELLP-syndrome)**
- **SIDS or ALTE in a family**
- **Recurrent acidotic, ketoacidotic, hypoglycemic, hyperammonemic crises**
- **A child with a known IEM in a family → investigation of all siblings**
- **Very strict veganism of the mother of a breast-fed baby.**

# Indications for selective screening

## Clinical symptoms (1)

- Poor sucking, inappetence, poor feeding
- Muscular hypotonia, hypo- or areflexia
- Recurrent vomiting, dehydration
- Lethargy, somnolence, **coma**
- Convulsions + other signs out of this list
- Dyspnoea, apnoea, hypothermia,
- Hepatomegaly
- Cardiomyopathy.

# Indications for selective screening

## Clinical symptoms (2)

- Unusual severe course of a gastrointestinal infection
- Exanthem, skin rash, conjungtivitis, alopecia
- A peculiar odour (sweaty feet, maple syrup, cabbage-, tomcat's urine-like, mousy smell)
- Reye or Reye-like syndroms.

# **Indications for selective screening**

## **Clinical symptoms (3)**

- **Symptoms as in pyloric stenosis but with acidosis (and not alkalosis)**
- **Sepsis- or meningitis-like symptoms but without bacteriological or serological findings**
- **Failure to thrive and psychomotor retardation.**

# Indications for selective screening

## Neurological signs

- Progressive psychomotor retardation
- Macrocephaly
- Metabolic stroke
- Progressive ataxia
- Muscular hypotonia
- Dystonia, athetosis
- Myoclonus
- Myopathy
- Myoclonic intractable seizures
- Progressive peripheral neuropathy
- Pyramidal signs, paraspasm, cerebral palsy
- Speech retardation
- Congenital cerebral malformations.

# **Indications for selective screening**

## **Multisystemic diseases**

- **Hepatosplenomegaly**
- **Chronic or recurrent pancreatitis**
- **Recurrent severe infections**
- **Non-immune hemolytic anemia.**

# Indications for selective screening

## Routine laboratory parameters (1)

- Unexpected metabolic acidosis/ketoacidosis
- Unclear hypoglycemia
- Hyperammonemia
- Elevated transaminases
- Lactic acidemia/-uria,  $\uparrow$  lactate/pyruvate quotient: PDHCD, defects of gluconeogenesis, mitochondriopathies. Most often secondary!!!
- Elevated anion gap ( $> 20$  mmol/l).

# Indications for selective screening

## Routine laboratory parameters (2)

- Unexplained leuco-, thrombo-, pancytopenia
- Unclear non-hemolytic anemia
- Hyperuricemia, hyperuricuria
- Hypouricemia, hypouricuria
- Hyperglycinemia, hyperglycinuria.

# Selective screening methods (to detect as broad a range of diseases as possible)

- Ion exchange column chromatography
- High performance liquid chromatography (HPLC)
- Gas chromatography-mass spectrometry (GC-MS)
- Tandem mass spectrometry (T-MS)
- Other methods
- Biochemical, molecular genetic methods.

# Material to be investigated by selective screening

- Freshly voided urine
- Freshly voided and deep frozen urine
- Freshly voided urine dried on filter paper (ca. 4 ml on 4 x 4 cm)
- Blood and serum on a Guthrie card.

# **Where to send the samples for selective screening**

- **Stoffwechsellabor, Zentrum für Kinderheilkunde und Jugendmedizin, Univ.-Klinikum Freiburg, Mathildenstr.1, 79106 Freiburg, Germany**
- **Dr. D. Matern, Division of Laboratory Genetics, Mayo Clinic, Rochester, MN, USA**

# Examples of IEM with acute life-threatening presentation

- Organic acirurias
- Urea cycle disorders
- Maple syrup urine disease (MSUD)
- Nonketotic hyperglycinaemia
- Disorders of mitochondrial fatty acid beta-oxidation.

# Initial laboratory blood investigations in patients with life-threatening presentation

- Blood gases ( pH,  $p\text{CO}_2$  ,  $\text{HCO}_3^-$ ,  $p\text{O}_2$  )
- Electrolytes (bicarbonate, anion gap)
- Ammonia
- Glucose
- Ketone bodies (3-HBA, acetoacetate, acetone)
- Uric acid
- Creatine phosphokinase (CPK)
- Lactate, pyruvate
- Complete blood count.

# **Initial laboratory urine investigations in patients with life-threatening presentation**

- **Ketone bodies (acetone, acetoacetate)**
- **Reducing ability (sugars)**
- **Dinitrophenyldrazine test (other ketones)**
- **Sulfite test**
- **Benzidine test (haemo- and myoglobine).**

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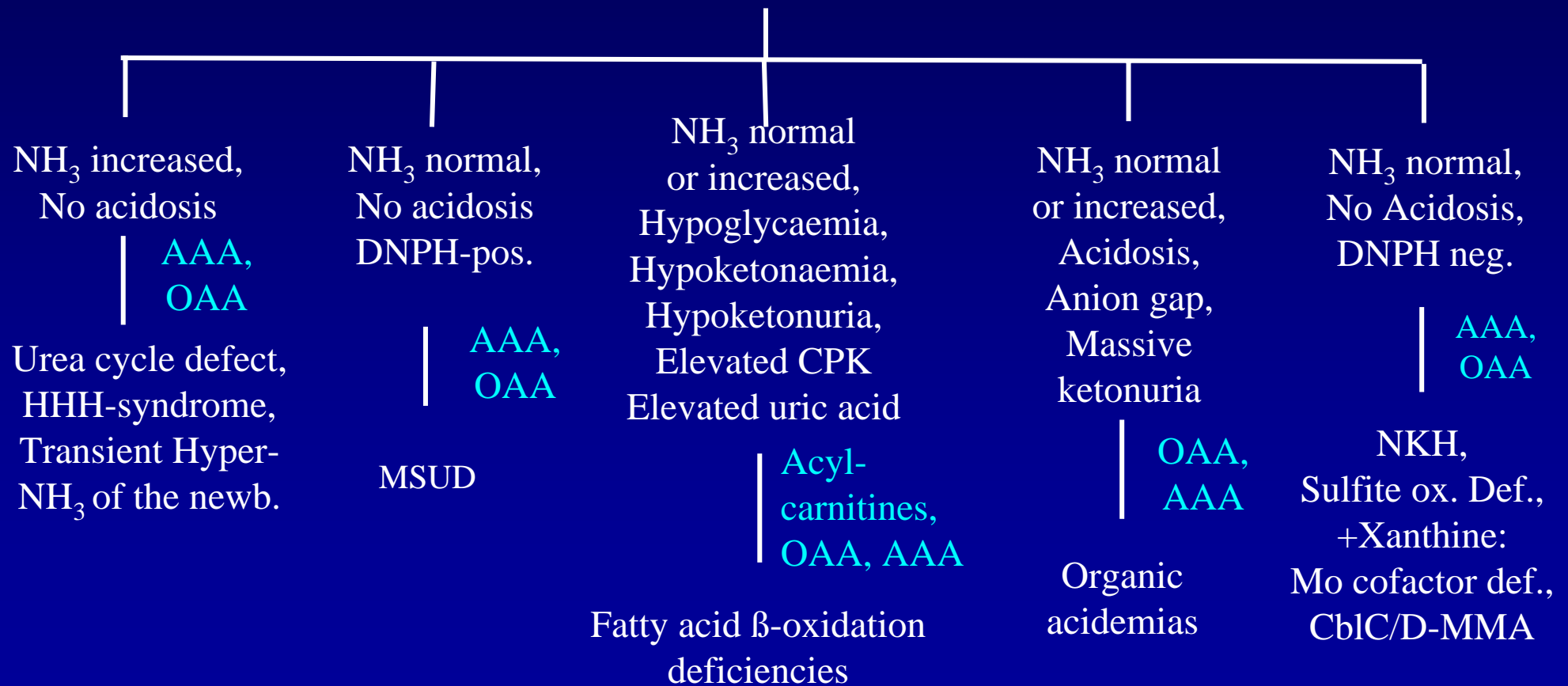
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# Algorithmic approach towards the diagnosis of the neonate in coma

## Routine laboratory investigations



Please notice my more extensive  
paper on selective screening for  
IEM and the principles of therapy  
in LITHUANIAN LANGUAGE:

Pediatrija 2003(5), 56-62

Thank you very much for your attention

