

Neonatal Screening

I - INTRODUCTION

- 1- Neonatal screening for a metabolic disease must address a frequent pathology for which there is an efficient treatment and only if this treatment is applied early in life.
- 2- The screening must be universal
- 3- Urine sample screening test

II - PHENYLKETONURIA

- 1- Epidemiology
- 2- Physiopathology
- 3- Hyperphenylalaninemia
- 4- Dihydropteridin reductase deficiency
- 5- Hyperphenylalaninemia can be detected after a few of days of normal feeding
- 6- Clinical forms, differential diagnosis
- 7- Treatment
- 8- Dihydropteridine reductase deficiency

[version pdf](#)

III - CONGENITAL HYPOTHYROIDISM

- 1-Epidemiology
- 2-Neonatal screening
- 3-Dosage methods
- 4- Treatment

IV COROLLARY

- 1- Overview of international practices
- 2- Overview of diagnosable diseases
- 3- Treatment
- 4- Diseases with apparent symptoms during the post natal period
- 5- Genetic counselling / informed consent
- 6- Development

*

I - INTRODUCTION

1- Neonatal screening for a metabolic disease must address a frequent pathology for which there is an efficient treatment and only if this treatment is applied early in life.

The universal screening of phenylketonuria and hypothyroidism are good examples of this concept.

Those are diseases that affect approximately 1 out of 10,000 neonates,

- leading to a serious encephalopathy during the neonatal period if no efficient treatment is applied and for which there are screening tests that are:
- specific,
- sensitive,
- not costly and to which there is a good response,
- this leads to the establishment of regional and national infrastructures,
- including accredited specialized laboratories.

2- The screening must be universal

- unless otherwise specified all newborns must have access to the program
- the laboratory personnel and the clinicians analyse results, control positive and dubious results, carry on the necessary investigations and establish a treatment,
- in practice: these tests are performed at the time of discharge of the mother from the maternity, (between the 2nd and 7th day after delivery,
- the metabolic disorder is then diagnosable,
- before any clinical sign appears in the newborn,
- the blood is drawn by heel prick on a filter paper identified with the newborn hospital card vital information.

3- Urine sample screening test

- a few health services have adopted the urinary screening that is done around the 3rd week of life from a filter paper containing a urine spot taken from a damp diaper. The dried filter paper is mailed to the screening centre by the parents.
- this urinary screening test was initiated in the Province of Quebec in the early seventies; it is one of the few programs that exist in the world. It allows the early detection of organic acid disorders, or other disorders which could have been missed by the blood tests done during the first week of life if the protein intake was insufficient to reveal a metabolic block.

II - PHENYLKETONURIA

1- Epidemiology

- autosomal recessive disease,
- risk of recurrence : $\frac{1}{4}$,
- q gene frequency = 1%,
- frequency of affected homozygotes: $q^2 = 0.06$ to 0.1%.

2- Physiopathology

- phenylalanine hydroxylase deficiency,
- a classical form that is treatable.

3- Hyperphenylalaninemia

- increase in number of catabolites of Phenylalanine (Phe),
- deficit of metabolites downstream to the enzyme (tyrosine, dopa, melanin...).

4- Dihydropteridin reductase deficiency

- severe form with:
- hyperphenylalaninemia, and hypertyrosinemia,
- serotonine and norepinephrenine deficiency downstream to this enzyme
- evolution without treatment:
within a few weeks digestive problems, skin lesions and convulsions are observed, with a delay in psychomotor development, deteriorated general health leading to death in absence of treatment. One must obtain blood and urine samples and a liver biopsy for a post mortem diagnosis and early treatment of a close relative, undiagnosed brother or sister. If the treatment was instituted too late the child will develop a profound psychomotor retardation (IQ= 29 to 50) a with a number of neurological disorders and hypopigmentation.

5- Hyperphenylalaninemia can be detected after a few of days of normal feeding

- normal Phenylalanine level < 4mg/100 ml (Other ref: <300mM),
- the test result is available within 15 days,
- automated fluorometric blood dosage of phenylalanine.

Note : the tests will detect hyperphenylalaninemia but not its cause: it could be a true enzymatic deficiency or transitory, (prematurity manifested by hyperphenylalaninemia and hypertyrosinemia or excess nutritional phe intake). The diagnosis must be confirmed by more precise blood tests.

6- Clinical forms, differential diagnosis

- Deficit in dihydropteridine reductase: hyperphenylalaninemia,
- <20mg/100ml; rapid lowering of Phe level with the diet but unpreventable neurological deterioration.

7- Treatment

- Phenylketonuria.
Hypoprotein diet with a low Phe content to assure the child will have the intake needs in Phe (to avoid overloading or deficit....biological control: 3mg/100ml < Phe < 10mg/100ml (other ref: 100mM to 300mM)
- Neonatal diet
Low Phe diet during infancy and if possible kept during adulthood; strict control of mother's Phe level: if it is too high during pregnancy there is an increased risk of foetal demise.

8- Dihydropteridine reductase deficiency

Treatment : substitution by tryptophane and serotonin, close follow up, genetic counselling and psychological aid.

III - CONGENITAL HYPOTHYROIDISM

1-Epidemiology: 0. 03 to 0.06 % births

2-Neonatal screening

In most programs TSH is measured on filter papers. If TSH is elevated the diagnosis must be confirmed with plasma measurements (TSH, free T4, total T3)

3-Dosage methods

- Dosage of TSH (thyroid stimulating hormone),
normal level < 12 μ U/ml ; pathological level > 30 μ U/ml ; intermediate level 15-30 μ U/ml : control indicated.
- Dosage of T4 (thyroxine or Tetraiodothyronine) by radioimmunoassay.
- Identifies all thyroid primary and secondary deficits but presence of false positive, (3% of positive results are detected by this method).
- Hypothalamo-hypophysary disorders are not detected by this method
- Confirmation by complementary tests: scintigraphy and measure of maternal thyroid antibodies and dosage of thyroglobulin.

4- Treatment :

Initially 10 μ g/kg de L Thyroxine with periodical controls of thyroid function every 3 months until one year of age then every 6 months until three years of age and thereafter every year.

IV COROLLARY

1- Overview of international practices

An overview of measures taken throughout the world confirms that neonatal screening was initiated in several countries in different ways and in most cases in

relation to the populations more at risk to develop a metabolic disease like phenylketonuria hypothyroidism and / or cystic fibrosis (mucoviscidosis). This is particularly true for blood dyscrasias such as sickle cell anemia and thalassemia, two diseases that are more frequent in the Mediterranean countries, Africa and Asia. Tyrosinemia is frequent in Finland and the Quebec Saguenay region. This implies that specific screening tests are developed according to the mutant gene frequencies found in certain populations that often live in isolates. Neonatal screening programs have been adopted by several countries. For instance neonatal screening for phenylketonuria and hypothyroidism are current practice in several countries of North America, Europe, in Japan New Zeland, Australia, Israel and more recently in China and South America (WB Hanley, personal communication).

TANDEM MASS SPECTROMETRY

The development of tandem mass spectrometry (MS/MS) has allowed in recent years the detection, confirmation of diagnosis and the follow up of newborns affected with phenylketonuria, hepatorenal tyrosinemia and MCAD (medium-chain acyl co-enzyme A dehydrogenase) deficiency and will probably be a screening tool for several metabolic disorders such as organic acidurias and urea cycle defects.

2- Overview of diagnosable diseases

Approximately 2 to 40 metabolic diseases can be detected in the neonatal period. The majority are in need of medical intervention, some will need a close surveillance.

- Hereditary metabolic diseases :Phenylketonuria, hepatorenal tyrosinemia, organic aciduria, fatty acid oxidation defects,....
- Blood dyscrasias : Thalassemia, sickle cell anemia
- Endocrine diseases : Hypothyroidism, adrenal hyperplasia
- Infectious diseases : Human immuno deficiency virus (HIV)
- Others:
 - Hearing deficit
 - Cystic fibrosis (mucoviscidosis)
 - Duchenne muscular dystrophy

i- Hearing deficit

It is generally accepted that neonatal screening can apply to non metabolic diseases like hearing deficits.

A number of health services have initiated hearing evaluation by otoacoustic emissions in the neonatal period for newborns aged from 30 months of gestation to full term.

This neonatal screening for hearing has the same goal as the screening programs for cystic fibrosis and Duchenne muscular dystrophy(DMD) that is to minimize secondary effects of evolutive diseases.

ii-Cystic fibrosis

In cystic fibrosis a diagnosis made in the early infancy allows the introduction of a special diet: studies have shown an improvement in the general health and growth of the patient.

The incidence of cystic fibrosis being between 1 in 2000 to 1 in 4000 births, this screening program has been adopted by several health authorities. A family study and genetic counselling are applied.

iii-Duchenne Muscular dystrophy (DMD)

In muscular dystrophy the advantage of an early treatment does not seem as efficient since the age of onset of the disease is variable and often the motor symptomatology is non specific and may be similar to certain orthopedic disorders. In the future an improved detection method, reducing positive and negative results, would allow to reconsider the indication to screen for DMD in the neonatal period.

iv-Immunodeficiency virus (HIV)

The screening for the immunodeficiency virus (HIV) in the neonate is controversial on ethic and clinical grounds. Although the early treatment of the newborn who is a virus carrier seems to prevent the acquired immunodeficiency syndrome several groups contest the universal neonatal screening for the virus since there is an elevated risk of individual and ethnic discrimination.

3- Treatment

Following biochemical, enzymatic and molecular studies that confirm the diagnosis a treatment is applied :

i- Dietary restrictions, special products, supplements....., food banks

As shown in phenylketonuria the alimentary restrictions and special foods will prevent overloading of catabolites deleterious to the child development. Protein or specific amino acid restrictions are indicated in most metabolic diseases. Food banks are generally under the state supervision and are responsible for the availability of special foods to the patient.

ii- Replacement therapy

- organs: the patient may be in need of an organ replacement like the liver transplantation in hepatorenal tyrosinemia in addition to a special diet. However in this particular disease the introduction of NTBC ((2-(2nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione)) stops an enzyme in the tyrosine metabolism leading to the decrease of succinylacetone that is toxic for the liver and responsible for severe neurological effects. This therapeutic approach has totally change the treatment of this disease in addition to eliminating a risky and costly liver transplant, and improving the patient well being and survival.

- enzymes, proteins: the replacement of enzymes and proteins is under development and evaluation of its therapeutic potential. For example a small number of patients suffering from Hurler or Hunter diseases, two mucopolysaccharidoses with a severe prognosis have been treated with synthetic enzymes but the beneficial effects of this procedure are limited. The enzyme replacement therapy combined with the recombinant human α -L-iduronidase in Hurler syndrome is nevertheless encouraging and further trials are planned. The enzyme replacement therapy can be done with normal bone marrow transplantation from a compatible donor. Replacement of proteins like globulins and insulin are also good examples of replacement therapy.

iii-Gene therapy

The introduction of a gene in a patient, with an appropriate vector to correct an abnormal metabolism. This domain is under sustained research particularly in cancerology and in the study of hereditary degenerative diseases

4- Diseases with apparent symptoms during the post natal period

- hypertrophic cardiopathy
- acyl-CoA deficiency
- hyperammonemia
- intermittent leucinosi
- others....

One may identify among hereditary diseases those for which the symptomatology is absent in the neonatal period but appears later during infancy or in adolescence and those that have a true late age of onset during adulthood.

Among metabolic diseases with late manifestations one notes the intermittent leucinosi that has a residual enzymatic activity enough to delay the appearance of symptoms if there is no increase in intake of food containing branched chain aminoacids. An infectious disease in the child may trigger typical manifestations of this disease commonly called maple syrup urine disease because of the urine odour.

5- Genetic counselling / informed consent

Access to neonatal screening in a modern society is primordial. However for economical reasons or expertise disponibility all newborns will not be tested. The number of diagnosable diseases has increased in recent years and this stresses the importance at least to identify populations that are more at risk to develop a disease. Parents' consent for the screening test is not obligatory in all states. There are a number of policies regarding the access to the test. According to countries and regions a neonatal screening test informed consent may be:

- i. mandatory,
- ii. mandatory with option to refuse the test or
- iii. optional.

If the screening test is positive a genetic counselling is offered to parents in view of a future pregnancy and, if they agree, to other family members identified as individuals at risk. A prenatal diagnosis can also be offered if a diagnosis can be reached by studying amniotic fluid or cells.

6- Development

Who will assume the development cost of these programs ? In general the state is responsible and must also see to the follow up of patients who had a positive screening test, to the long or short term appropriate treatment, and the genetic counselling to be offered to the parents of the positively screened individuals. The institution or other accredited organism is also responsible to the development of screening techniques and their validation.

The use of tandem mass spectrometry leads to new therapeutic approaches, increase the survival of children for whom a diagnosis is made early who will eventually rely on the take over by adult medicine services.

Ethics committees and the scientific community may be invited to study the merit of new disease screening methods developed and proposed by research groups: it is then the duty of ethic committee members to formulate an advice in consultation with the population on the pertinence of introducing new screening tests.

Contributor(s)

Written 05- Louis Dallaire, Jean-Loup Huret
 2005

Citation

This paper should be referenced as such :

Dallaire L, Huret JL . Neonatal Screening. Atlas Genet Cytogenet Oncol Haematol. May 2005 .

URL : <http://AtlasGeneticsOncology.org/Educ/NeonatID30056ES.html>

© Atlas of Genetics and Cytogenetics in Oncology and Haematology
