Phenylketonuria

HISTORY OF PRESENTING ILLNESS:

- PKU-affected infant is typically **ASYMPTOMATIC**
- PKU **diagnosed as result of standard newborn screening** (Guthrie test) for phenylalanine (normal level <200 µmol/L.) Atypical PKU may produce some early neurological symptoms.

UNTREATED PKU (later in life) may present with:

- Failure To Thrive (if unscreened infant is presenting early in childhood)
- Eczema
- Significant mental retardation (mean IQ =45)
- Spasticity
- Tremors
- Abnormal gait
- Seizures
- Autistic features
- Lighter complexion (type 1, blue eyes blond hair fair skin)
- a characteristic "mousy" odor that results from the accumulation of phenylacetic acid (on skin, breath, urine)

MATERNAL PKU affects only the children of mothers whose PKU is untreated or mismanaged.

Such children may present with:

- Poor growth
- Microcephaly
- Intellectual developmental delay
- Abnormal facial appearance
- Congenital heart disease (patent ductus arteriosus, blood flowing out of the aorta back into the lungs)

DIFFERENTIAL DIAGNOSES for infant presenting with elevated blood [Phe] levels

- Classical PKU
- Atypical (malignant) PKU
- Maternal PKU
- False positive on Guthrie Test

FINDINGS IN HISTORY:

Nil relevant (unless one or both parents are homozygous PKU sufferers)

EXAMINATIONS

PKU cannot be diagnosed clinically in neonates (requires blood test)
Untreated PKU may be diagnosed clinically as a generalised nerve dysfunction and/or developmental delay (see HPI)

TESTS AND INVESTIGATIONS

- ***Guthrie Blood Test:*** part of standard neonate screening;
- 50% false positives but NEVER FALSE NEGATIVES
  - Blood is collected by heel-prick onto a piece of blotter-paper (Guthrie card);
  - The blood is then placed on a culture dish which contains a species of bacteria which require phenylalanine for growth
  - In normal children's blood there isnt enough phenylalanine to support growth.
  - Other blood tests may also detect elevated levels of phenylpyruvate, phenylacetate, phenyllactate, phenylethylamine

  Second Guthrie Test must be performed to eliminate maternal PKU and false positives

*NOTE: [Phe] of infant in placenta is 1.5 x maternal plasma [Phe]- higher at birth because of immature liver enzymes

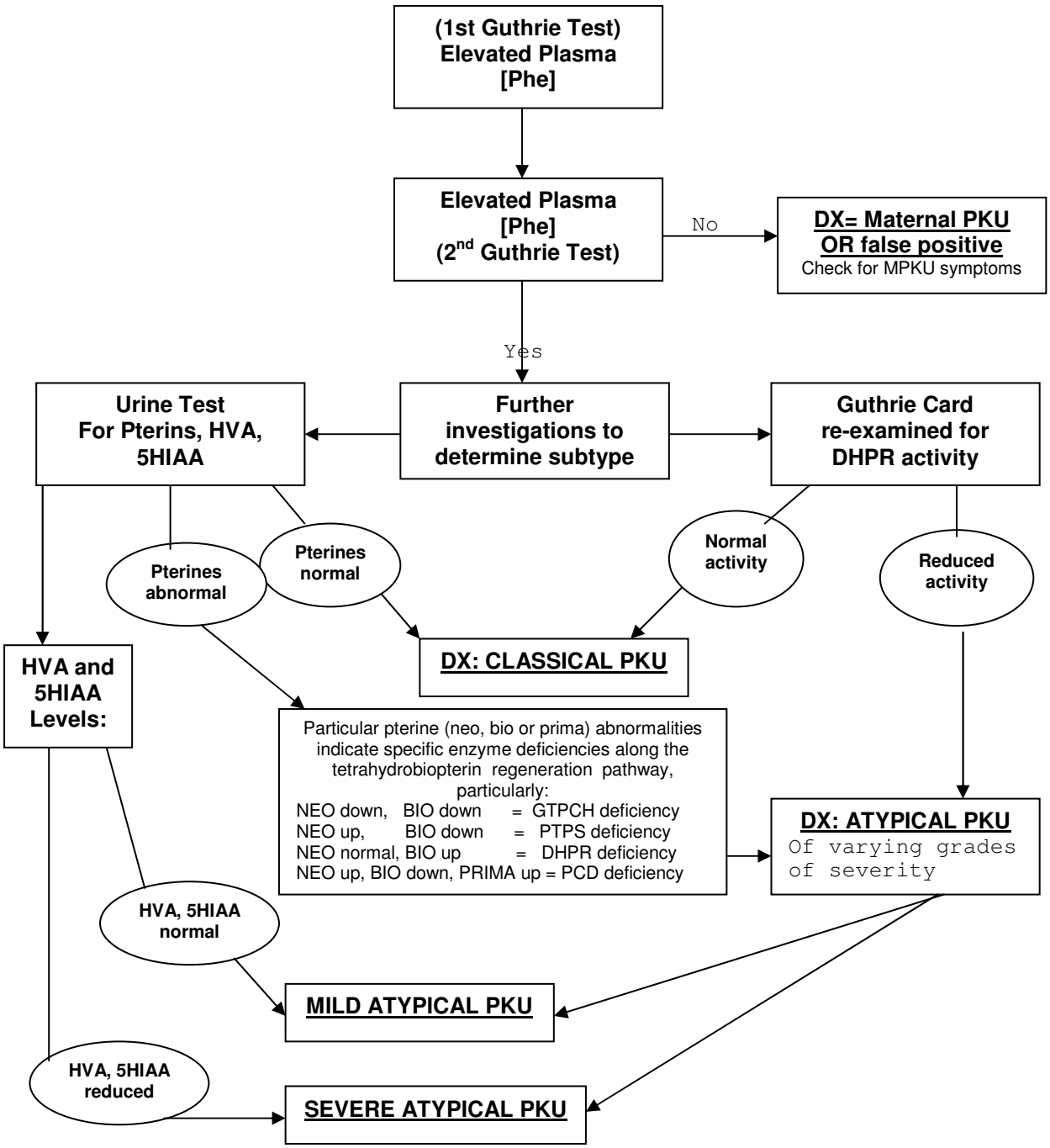
- **Urinalysis** is required to determine whether PAH is responsible, or its coenzyme BH4 (tetrahydrobiopterin)
  - This test measures the presence of:
- **Pterines (**neobiopterin , primapterin and biopterin**,** metabolites of tetrahydrobiopterin generation pathway**)**
- **HVA (**homovanillic acid**,** a major metabolite of dopamine generation pathway**)**
- **5HIAA** (5-Hydroxy indole acetic acid; major metabolite of serotonin generation pathway)

DHPR **Dihydropteridine (DHPR) reductase activity** measured from original Guthrie screen card

- (it is an enzyme that converts dihidrobiopterin into tetrahydrobiopterin)

PRENATAL diagnosis can be made via fetal liver biopsy- but this is rarely justified

How is the diagnosis made: Diagnostic Decision Tree



MANAGEMENT:

INITIAL MANAGEMENT:

- referral to metabolic dietician, PKU specialist and social worker (genetic councillor if available)
- PARENT EDUCATION: emphasis on normality
  - Baby will develop normally so long as the diet as followed
  - information about the biochemical and genetic basis of PKU, and the importance of appropriate dietary treatment
  - the basic principles of dietary management(i.e introduce the Phe Unit; being 15mg of Phe)-
  - …and AVOIDING ASPARTAME (ARTIFICIAL SWEETENER)

CLASSICAL:

first 48 hrs:

- mother expresses milk for storage.
- Baby is fed a phenylalanine-free formula from a bottle
- Phenylalanine levels should FALL (another Guthrie test is performed)

Breast Feeding Regimen:

- Baby is fed a set volume of formula (eg. XP Analog ™) and then breast-fed to satiety

(breast milk is low in Phenylalanine)

- **Bi-weekly** blood tests **for first 2 weeks** are performed to monitor Phe levels;
  - accept 120-360 micromol. per litre
- **Weekly tests** until 6 weeks old
- **Fortnightly** until 3 months
- Introduce solid food at 4-6 months:
  - **REST-OF-LIFE DIET:** Limit protein in diet; replace all meat/fish/dairy products with
  - specialised FORMULA; avoid nuts, beans, eggs
  - Reduce intake of protein rich vegetables eg mushroom, broccoli, potato. Increase intake of refined fats, starches and carbohydrates.
  - ENSURE ADEQUATE VITAMIN INTAKE for proper growth
- **Fortnightly Blood Tests**
- **Monthly Visits to PKU clinic** until 1 year old
- **Long term Dietary Management;** visit PKU clinic 4 times year to monitor developmental milestones

ATYPICAL: must be managed with a view of the specific enzyme deficiencies; products of the malfunctioning enzyme pathways (eg L-dopa, serotonin etc.) must be SUPPLEMENTED in the diet. Otherwise the diet and management are the same as for classical PKU

DISEASE DEFINITION:

- A genetic abnormality of phenylalanine homeostasis can result in pathological elevations of blood phenylalanine, which if persistently high could result in permanent neurodevelopmental impairment.

EPIDEMIOLOGY:

- INCIDENCE 1 per 10,000 births in NSW; occurs in ALL ETHINC GROUPS
- 98% of PKU is CLASSICAL
- there is a continuum of severity in effects with no real distinction
- More common in Turkey (1 in 2500 births)
- Less common in Scandinavia and Japan (approx 1 in 100,000 to 200,000)

AETIOLOGY / GENETICS

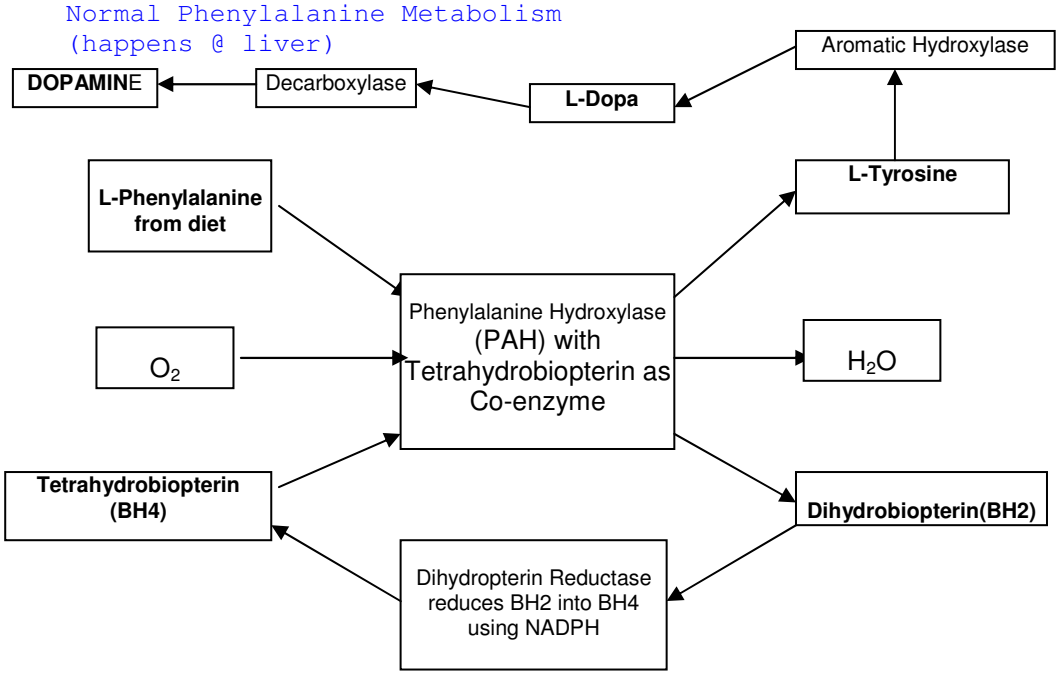
- PKU is an *autosomal recessive mutation* on chromosome 12. The classical form of the disease results from a mutation which leads to amino acid substitutions.
- Both parents genes need to be of the PKU type before the disease will manifest itself.
- The disease does not show itself until the individual has left the womb. Before this, the mothers enzymes will break down the Phenylalanine, as soon as the child leaves the womb however it's own enzymes are incapable of taking over the job, and the child's levels of Phenylalanine will begin to build up.
- The build-up of phenylalanine will inhibit the activity of a myelin-protecting enzyme
- This will result in gradual demyelination, a “digestion” of the myelin sheath with subsequent loss of nerve transmission efficiency; this results in tremors and may affect gait.
- A lack of tyrosine results in a deficiency of neurotransmitters, which in turn leads to decreased mental function, autism, spasticity and seizures.

PROGNOSIS:

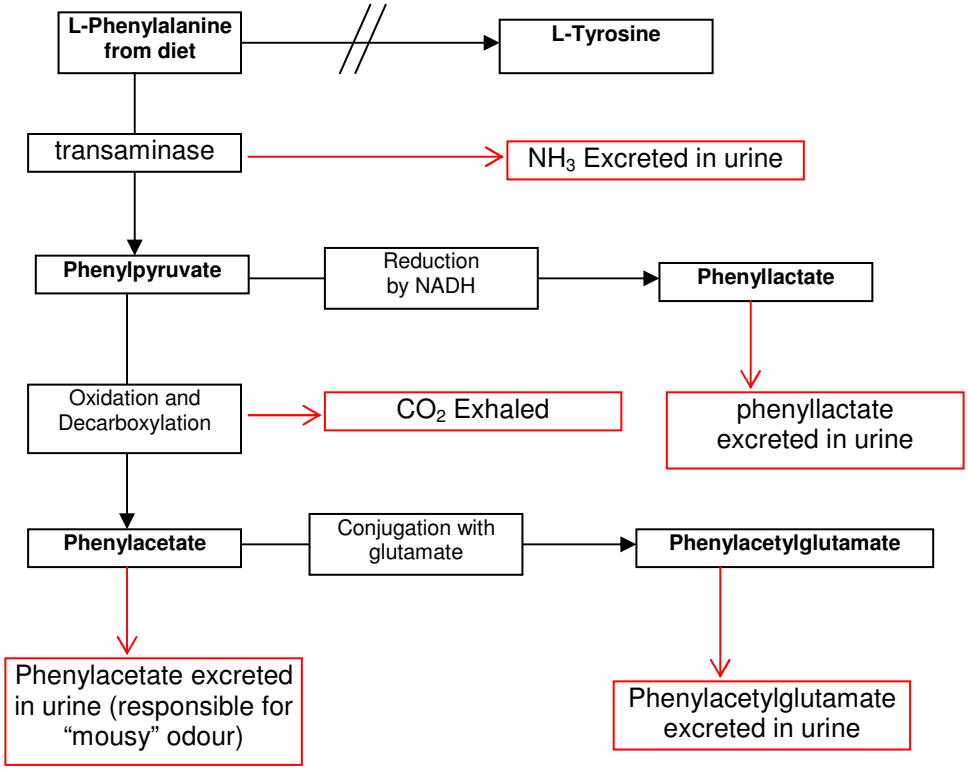
- Well managed PKU will never become symptomatic. Otherwise, the demyelination of nerves and deficiency in neurotransmitters will lead to mental developmental delays.

BASIC SCIENCES: BIOCHEMISTRY

Normal Phenylalanine Metabolism (happens @ liver)



ABNORMAL PHENYLALANINE METABOLISM



BASIC SCIENCES: GENETICS: PRINCIPLES OF HUMAN INHERITANCE

Autosomal disorders are relevant only to the 22 non-sex chromosomes (not X or Y)-eg. Downs syndome

For recessive disorders, expression is altered only when both alleles of a particular gene are different from the normal gene

penetrance is the likelihood that a given gene will have any expression at all

Monogenic disorders are detrmined by a single mutant gene (aka. Mendelian disorders)- eg. Huntingtons, cystic fibrosis

Mendelian disorders can be either autosomal recessive, autosomal dominant or X_linked (an example of x-linked disorders is fragile X mental retardation syndrome)

- a mutation in a gene can result in a defective protein that can lead to a diverse range of phenotypic effects, called **pleiotropy (eg. in PKU)**

IN PKU, the mutations are usually **missense mutations** (single amino acid deletions or substitutions) and s**plice site mutations** (incorrect sites of RNA primary transcript, i.e the RNA reads starting from the wrong amino acid codon). Large gene deletions are not common.

DEVELOPMENTAL MILESTONES: can be grouped into 4 areas:

- Gross motor –
  - rolls over from supine at 4.5months,
  - sits unaided at 8 months crawling at 9months,
  - stands bearing weight at 6months,
  - walks around 1year, jumps at 3
- Vision and Fine Motor-
  - Grasps cube at 5months,
  - Tower of 2 blocks at 6 months
  - Tower of four blocks at 27 months
  - Follows finger with eyes to 180 degrees at 4 months
  - Can pick up spilled "hundreds and thousands" at 7 months
  - Palmar grasp at 6 months, mature grasp by 1year
  - Scribbles with a crayon at 2 years
  - Thumb-finger grasp at 11 months
- Language and Hearing
  - Responds to bell at 2 months
  - Turns to bell at 4 months
  - Able to repeat whispered words at 3 years
  - Vocalising at 2 months
  - "mumma" and "dadda" at 10 months
  - knows plural by 3 years
- Social Skills and understanding
  - Smiles socially at 4-6 weeks
  - Shyness at 10 months
  - Puts on clothing at 3 years
  - Dresses self at 5 years

PSYCHOSOCIAL ASPECTS OF PKU:

Major Factors:

- Parental resources eg. mental health, self-esteem, ability to understand the cndition
- Family environment (cohesion, stability, low level of conflict)
- Shared responsibilities
- Support network
- Availability of material resources

Dealing with the diagnosis:similar to grief response, eg. denial, grief or anger. Adjustment follows from crisis to acceptance.

Coping styles associated with positive adjustment:-

- Emotional (relief and support through talking and expressing feelings)
- Action-oriented (coping by planning, taking actions, solving problems and seeking information)
- Thinking-oriented (support and aceptance through understanding the problem)

Therefore EDUCATION IS CRUCIAL; many will also benefit from social support from social workers and other families with PKU.