Paediatric Palliative Care
From Metabolic physician perspective

Hong Kong Society of Children’s Palliative Care Annual Symposium 2019
Terminology

- Metabolic diseases
- Inborn errors of metabolism (IEM)
- Inherited metabolic diseases (IMD)
- Rare diseases
- Orphan diseases
**Inborn errors of metabolism (IEM)**

- Individually – very rare
- Collectively common group of disorders affecting ~ 1 in 4000 births
- > more than 1000 identified IEMs
- List continuously increasing

- Variable presentations
- Chronic progressive vs acute rapid deteriorating clinical course
- Mild to severe
- Subtle to overt

- Newborn screening has been life saving for some
Inborn errors of metabolism (IEM)

- Defect in a metabolic pathway

A \[\text{enzyme}\] B

**Symptoms of Intoxication**

A \[\text{enzyme}\] C \[\text{enzyme}\] B

**Symptoms of Deficiency**
Therapeutic Approaches for IEM

- Substrate Deprivation
- Externally supplement the deficient product
- Stimulating an alternative pathway
- Providing a vitamin co-factor
- Replacing an enzyme
- Organ Transplant
- Gene Therapy
Some IEMs are easily treated with simple measures like drugs, dietary manipulation.
Scaly skin rash 鱗屑疹
<table>
<thead>
<tr>
<th>Age of onset</th>
<th>Presenting symptoms</th>
<th>Investigations (urine)</th>
<th>Confirmatory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1y</td>
<td>• generalised</td>
<td>• ↑ lactate</td>
<td>• defective activity of holocarboxylase synthetase (cultured fibroblasts)</td>
</tr>
<tr>
<td></td>
<td>erythematous scaly</td>
<td>• 3OH isovalerate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>skin eruption</td>
<td>• 3 methyl-crotonyl-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(guttae psoriasis)</td>
<td>glycine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• episodic metabolic acidosis</td>
<td>• 3 OH propionate (multiple carboxylase deficiency)</td>
<td></td>
</tr>
</tbody>
</table>

Diagram shows the metabolic pathways involving biotin, biocytin, and holocarboxylase synthetase. The diagram highlights the interplay between dietary intake, gut flora, and the biological processes involving biotin, biocytin, and holocarboxylase synthetase. The genetic code shown includes sequences GTG, GTC, TGC, AGG, ATGG, and GAG, with 40 and 50 positions indicated.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple carboxylase deficiency</td>
<td>• biotin</td>
<td>• normal growth &amp; development</td>
</tr>
<tr>
<td>(Holocarboxylase synthetase deficiency)</td>
<td></td>
<td>• no further skin eruptions</td>
</tr>
</tbody>
</table>
Holocarboxylase Synthetase deficiency
合成酶缺乏症
Parents as well as Doctors’ wish

- if IEM can be diagnosed and treated early especially before they become ill, outcome can be much better and in some instances even life saving
Newborn screening – one effective way for early diagnosis of IEM

- Newborn screening is the **early** identification of infants affected by certain diseases which may not be apparent at birth
- Screen every newborn baby at birth
- **preventive** health measure
- detects disorders that, if left untreated, can cause death, disability, intellectual disabilities & other serious consequences
- If diagnosed early, these conditions can be successfully treated.
IEM common in Chinese

IEM with good treatment outcome

All IEM
1990’s Expansion of Newborn screening – screen for over 30 different IEMs in the newborn period

Tandem mass spectrometry (MS/MS) revolutionized newborn screening
Tandem Mass Spectrometry (MS/MS)

Multiplex testing

- simultaneous, rapid analysis & detection of many disorders
- a high degree of precision & accuracy

3 mm

~ 2 hours

~ 2 minutes / sample

Data analysis
Hong Kong government set to test babies for inborn metabolic diseases at cost of HK$10 million a year

Government plans to benefit 50,000 newborn babies a year at a cost of HK$10 million in initiative unveiled in chief executive’s policy address

Emily Tsang
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Published: Sunday, 08 March, 2015, 11:56pm
Updated: Monday, 09 March, 2015, 6:02am

Chinese University has offered a screening programme for inborn metabolism problems since 2013 at a charge of HK$800 per test for 30 congenital errors, including fatty acid oxidation and organic acid disorders. Photo: Sam Tsang

A new screening programme for newborn babies announced in the policy address is likely to involve a blood test for 12 types of inborn metabolic diseases that affect one in every 3,000 local infants, the South China Morning Post has learned.

The neonatal screening test would cost the government at least HK$10 million a year at around HK$200 per test for the detection of congenital metabolic errors, according to a medical source. The tests would be carried out within 48 hours of birth.

The inborn disorders to be tested would include phenylketonuria (PKU), caused by an enzyme deficiency which could turn some protein-rich food or sweeteners into poisons for young sufferers, the source said.

It is expected to benefit around 50,000 newborn babies every year.

Elderly Healthcare Services

192. The HA will enhance healthcare services for elderly patients, including:

(a) finishing improvement works to barrier-free facilities in the remaining hospitals by the end of 2016, following completion of similar works in general outpatient clinics and acute hospitals at the end of 2014;
HKSAR Government
Newborn screening programme for IEM

- Announced in Chief Executive’s 2015 Policy address
- Task force set up in 2015
- Members from both Department of Health & Hospital Authority
- Obstetricians, Paediatricians, Chemical Pathologists, Clinical Geneticists, Maternity Child Health clinics
- Pilot study phase I
- Rolled out 1st Oct 2015 at 2 birthing units (QMH & QEH)
- Planning for extension into territory wide universal screening programme for all newborn babies in HK 2017-2018
<table>
<thead>
<tr>
<th>Screened Conditions with Metabolic newborn screening programme</th>
<th>Drug treatment</th>
<th>Special milk formulae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Multiple carboxylase deficiency</td>
<td>yes (biotin)</td>
<td>N</td>
</tr>
<tr>
<td>2 Glutaric acidaemia type I (GAI)</td>
<td>Yes (carnitine, riboflavin)</td>
<td>Y</td>
</tr>
<tr>
<td>3 Methylmalonic acidaemia (MMA)</td>
<td>Yes (carnitine, hydroxycobalamin)</td>
<td>Y</td>
</tr>
<tr>
<td>4 Propionic acidaemia (PA)</td>
<td>Yes (carnitine, biotin)</td>
<td>Y</td>
</tr>
<tr>
<td>5 Isovaleric acidemia (IVA)</td>
<td>Yes (carnitine, glycine)</td>
<td>Y</td>
</tr>
<tr>
<td>6 3-hydroxy-3methylglutaryl-CoA (HMG-CoA) lyase deficiency</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>7 Beta-ketothiolase deficiency/2-methylacetoacetyl-CoA thiolase (MAT) deficiency</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>8 Classic phenylketonuria (PKU)</td>
<td>Yes (BH4)</td>
<td>Y</td>
</tr>
<tr>
<td>9 6-pyruvoyl-tetrahydropterin synthase deficiency</td>
<td>Yes (BH4, sinemet, oxytriptan)</td>
<td>Y</td>
</tr>
<tr>
<td>10 Argininosuccinic acidemia</td>
<td>Yes (benzoate, arginine)</td>
<td>N</td>
</tr>
<tr>
<td>11 Maple syrup urine disease (MSUD)</td>
<td>Yes (thiamine)</td>
<td>Y</td>
</tr>
<tr>
<td>12 Citrullinaemia type I</td>
<td>Yes (benzoate, arginine)</td>
<td>N</td>
</tr>
<tr>
<td>13 Citrullinaemia type II (Citrin deficiency)</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>14 Tyrosinaemia type I **</td>
<td>Yes (nitisinone)</td>
<td>Y</td>
</tr>
<tr>
<td>15 Homocystinuria **</td>
<td>Yes (pyridoxine, folinic acid)</td>
<td>Y</td>
</tr>
<tr>
<td>16 Carnitine uptake deficiency</td>
<td>Yes (carnitine)</td>
<td>N</td>
</tr>
<tr>
<td>17 Carnitine-acylcarnitine translocase deficiency (CACT)</td>
<td>Yes (carnitine)</td>
<td>Y</td>
</tr>
<tr>
<td>18 Carnitine palmitoyltransferase II deficiency (CPTII)</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>19 Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>20 Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>21 Glutaric acidaemia type II (GAI)/Multiple acyl-CoA dehydrogenase deficiency (MADD)</td>
<td>Yes (riboflavin, carnitine)</td>
<td>Y</td>
</tr>
<tr>
<td>22 Congenital adrenal hyperplasia</td>
<td>Yes (hydrocortisone, fludrocortisone)</td>
<td>N</td>
</tr>
<tr>
<td>23 Biotinidase deficiency</td>
<td>Yes (biotin)</td>
<td>N</td>
</tr>
<tr>
<td>24 Classic Galactosaemia</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>17/24</strong></td>
<td><strong>14/24</strong></td>
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</table>
HKSAR Newborn Screening Programme for Inborn Errors of Metabolism

Chief Executive Policy address:
(study the feasibility of trying out in public healthcare system a screening program for newborn babies for IEM)

<table>
<thead>
<tr>
<th>Year</th>
<th>Pilot (Phase 1)</th>
<th>Pilot (Phase 2)</th>
<th>Extension into territory wide program in phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015/16</td>
<td></td>
<td>Pilot (Phase 2)</td>
<td></td>
</tr>
<tr>
<td>2016/17</td>
<td>Pilot (Phase 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017/18/19</td>
<td></td>
<td></td>
<td>Extension into territory wide program in phases</td>
</tr>
<tr>
<td>2020</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HA Hospitals</th>
<th>QMH QEH</th>
<th>QMH QEH</th>
<th>PWH TMH KWH</th>
<th>PMH PYNEH UCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>Term</td>
<td>All (including preterm &amp; sick term infants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of IEM</td>
<td>21</td>
<td>24</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>% of live births covered (HA)</td>
<td>&lt; 25%</td>
<td>25%</td>
<td>70%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Some IEMs can be treated by more complicated measures like Transplant or Enzyme replacement therapy
Mucopolysacharidosis type I (Hurler syndrome)

- presented with hump over back (lumbar gibbus)
- extensive mongolian spots
- bilateral inguinal hernia
Mucopolysacharidosis type I (Hurler Scheie syndrome)

- multiple joint contractures noted since birth
- developmental delay
- severe hearing loss
- coarse facial features

- sustained cervical cord injury with C1/2 subluxation after accidental fall
- internal fixation with bone graft and external halo jacket
Mucopolysaccharidosis type II (Hunter syndrome)

- presented with big head and developmental delay
- inguinal hernia
Mucopolysacharidosis type III (Sanfilippo disease)

- normal up until 6 y
- first presented with behavioural problems, aggressive behaviour & violence at school
- subsequently noted to have cognitive regression
- hypersomnolence during day time & refusal to sleep at night

MPS III - Neuropsychiatric presentation
- predominate CNS symptoms
- relative lack of somatic features as in other types of MPS
- no skeletal abnormalities
Mucopolysaccharidosis type VI (Maroteaux–Lamy syndrome)
The Multidisciplinary Treatment Team

- Pediatrician
- Otorhinolaryngologist
- Interventional Geneticist
- Surgeon
- Pulmonologist
- Orthopedist
- Cardiologist
- Anesthesiologist
- Neurologist
- Gastroenterologist
- Dentist
- Genetic Counselor
Supportive Treatment

Medical care to treat systemic conditions & improving the person's quality of life

- **Physical therapy** and daily exercise may delay joint problems and improve the ability to move

- **Tonsillectomy and adenoidectomy** may improve breathing among affected individuals with obstructive airway disorders and sleep apnea

- Sleep studies can assess airway status and the possible need for Bipap +/- nocturnal oxygen supplementation

- Some patients may require surgical insertion of a tracheostomy tube to aid breathing

- **Surgery for hernias repair, shunt operation** for obstructive hydrocephalus, and release of carpal tunnel syndrome

- **Corneal transplants** may improve vision among patients with significant corneal clouding
Treatment for MPS

- Supportive treatment
- Disease specific treatment options

**Hematopoietic stem cell transplant (HSCT)** (干细胞移植)

Healthy stem cells (from bone marrow or cord blood) are transplanted i.v. to provide normal enzyme producing cells to the patient

**Enzyme replacement therapy (ERT)**

A recombinant form of the deficient enzyme is infused i.v. at definite intervals
Hematopoietic stem cell transplant

- First attempted in the 1980s and mostly used for MPS I

- Provides metabolically competent cells which may correct the enzyme deficiencies

- Positive results when performed early in a disease's course, despite its challenges and risks
  - transplant failure or rejection
  - toxicity of the conditioning regimen
  - difficulty finding a good donor match
Post transplant MPS patients

- MPS VI
  - HSCT at 6y
  - HSCT at 2y9m
  - HSCT at 14m
  - HSCT at 5y
Post transplant MPS patients
ENZYME REPLACEMENT THERAPY (ERT)

- a medical treatment by giving the patient an intravenous (IV) infusion at regular intervals that contains the deficient or absent enzyme

- R&D began in the mid-1960s
- Clinical trials by the 1980s
- Advances in recombinant DNA manufacturing in the early 1990s enabled enzyme production in quantities large enough for commercial development
- the first ERT went on the market in 1991 for Gaucher type I

- currently available for: Gaucher disease, Fabry disease, MPS I, MPS II, MPS VI, Glycogen storage disease type II, MPS IV
Issues of concern with ERT

- ERT does not “cure” the underlying disease, only the symptoms

- data on survival benefit, drug efficacy continue to be accumulated from ongoing studies & patients registry

- cost-effectiveness:
  drug cost for ERT range between $ 0.5M - 4.4M / patient / year
• established 2005

• mutual support children & their families with rare diseases

• a strong advocate for enzyme replacement therapy for lysosomal storage diseases
Expert panel on Enzyme replacement therapy for rare metabolic diseases

Set up by Hospital Authority 2007
Panel members: HA administrators, Clinicians, Pharmacists
Regular meetings 3-4 times per year

- To oversee commissioning of the ultra-expensive ERT in HK
- To set up treatment guidelines on ERT for specific disease groups
- To review every new as well as renewal applications

LSD patients currently on ERT funded by HA (24 patients/2018)

MPS
- 2 MPS I
- 2 MPS VI

Other LSDs
- 10 Pompe (3 infantile, 7 late onset)
- 2 Gaucher
- 8 Fabry
Inborn errors of metabolism (IEM) Summary

- Individually – very rare
- Collectively common group of disorders affecting ~ 1 in 4000 births
- >more than 1000 identified IEMs
- List continuously increasing

- Variable presentations
- Acute rapid deteriorating vs chronic progressive clinical course
- Mild to severe
- Subtle to overt

- In the exciting new era of treatment for various IEM
- Simple measures: drugs, diet
- Complicated measures: Hematopoietic stem cell transplant, Enzyme replacement therapy

- Early diagnosis & treatment are keys to treatment success
- Newborn screening has been life saving for some
- On going research offer hope for newer/better treatment options
Some IEMs do not have effective treatment, run a progressive downhill course leading to premature demise
Mucopolyssacharidosis type I
(Hurler Scheie syndrome)

• Treated with ERT for 4 years (2012-16)

• Despite ERT, developed progressive severe valvular disease requiring open heart surgery

• Parents decided against cardiac operation & accepted withdrawal/termination of ERT

• Now receiving palliative care at Tuen Mun Hospital
Mucopolyssacharidosis type II (Hunter syndrome)

- received ERT for 2y (2011–13)
- progressive cognitive decline – severe phenotype
- ERT discontinued
- Palliative care since 2018
- Pending gastrostomy with increasing choking episodes
Mucopolysacharidosis type III (Sanfilippo disease)

- normal up until 6 y
- first presented with behavioural problems, aggressive behaviour & violence at school
- subsequently noted to have cognitive regression
- hypersomnolence during day time & refusal to sleep at night

**MPS III - Neuropsychiatric presentation**

- predominate CNS symptoms
- relative lack of somatic features as in other types of MPS
- no skeletal abnormalities
Mucopolyssacharidosis type III (Sanfilippo disease)

- Progressive deterioration in cognitive function
- Regress to mental age of 1–2 y by end of first decade
- Total dependent activities of daily living

- With relative lack of other extra CNS manifestations, patients can survive into adulthood 30–40y age

- caring for MPS III patients like caring adult size patients with a mental age of 1–2y
- +/- hyperactivity & aggression
IEM patients life journey – Role of Heath care workers

- Provision of care at different disease stages according to the needs of the patients & their families
- A continuum of care
- Team work (work hand in hand)
- Diagnosis -> ‘aggressive’ treatment -> failure of available treatment -> Palliative care
The Multidisciplinary Treatment Team

- Interventional Geneticist
- Pediatrician
- Surgeon
- Otorhinolaryngologist
- Orthopedist
- Anesthesiologist
- Gastroenterologist
- Genetic Counselor
- Dentist
- Neurologist
- Cardiologist
- Pulmonologist

Palliative care
IEM patients’ needs
- the rarity and complex nature of IEM requires an integrated specialised clinical & laboratory service to provide satisfactory diagnosis & management

HK Children’s Hospital
- a specialised tertiary care centre
- HKCH (Hub) - taking care of IEM patients & their families with hand in hand supporting stepdown care by regional hospitals (Spokes)

Our common Goal:
a brighter & more promising future for all IEM patients & their families, providing necessary treatment as well as supportive care that these patients & their families need