Paediatric Palliative Care From Metabolic physician perspective

Hong Kong Society of Children's Palliative Care
Annual Symposium 2019

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Hong Kong Children's Hospital
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Terminology

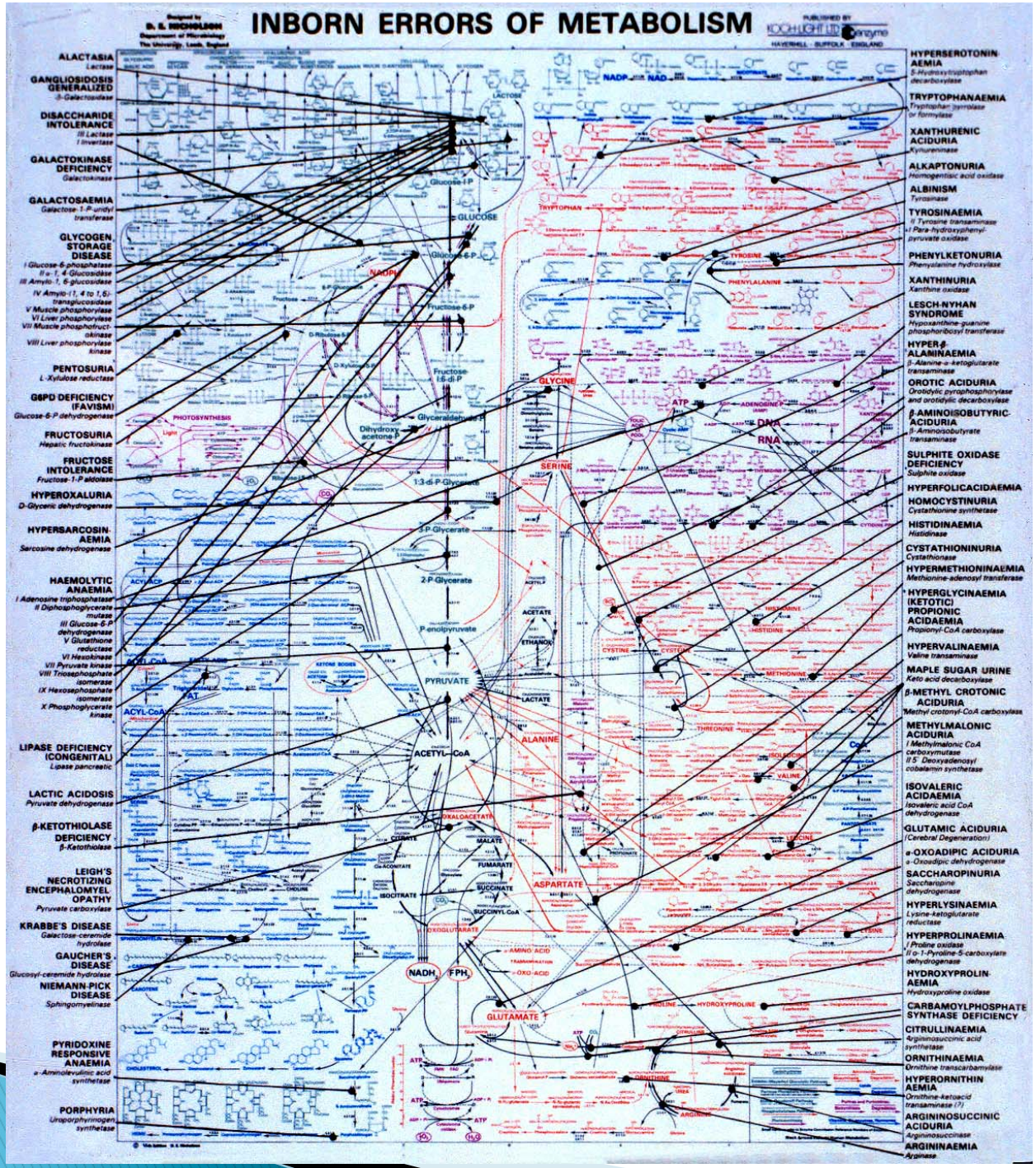
- Metabolic diseases
- Inborn errors of metabolism (IEM)
- Inherited metabolic diseases (IMD)
- Rare diseases
- Orphan diseases

Inborn errors of metabolism (IEM)

- Individually – very rare
- Collectively common group of disorders affecting ~ 1in 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
Designed by D. E. NICHOLSON
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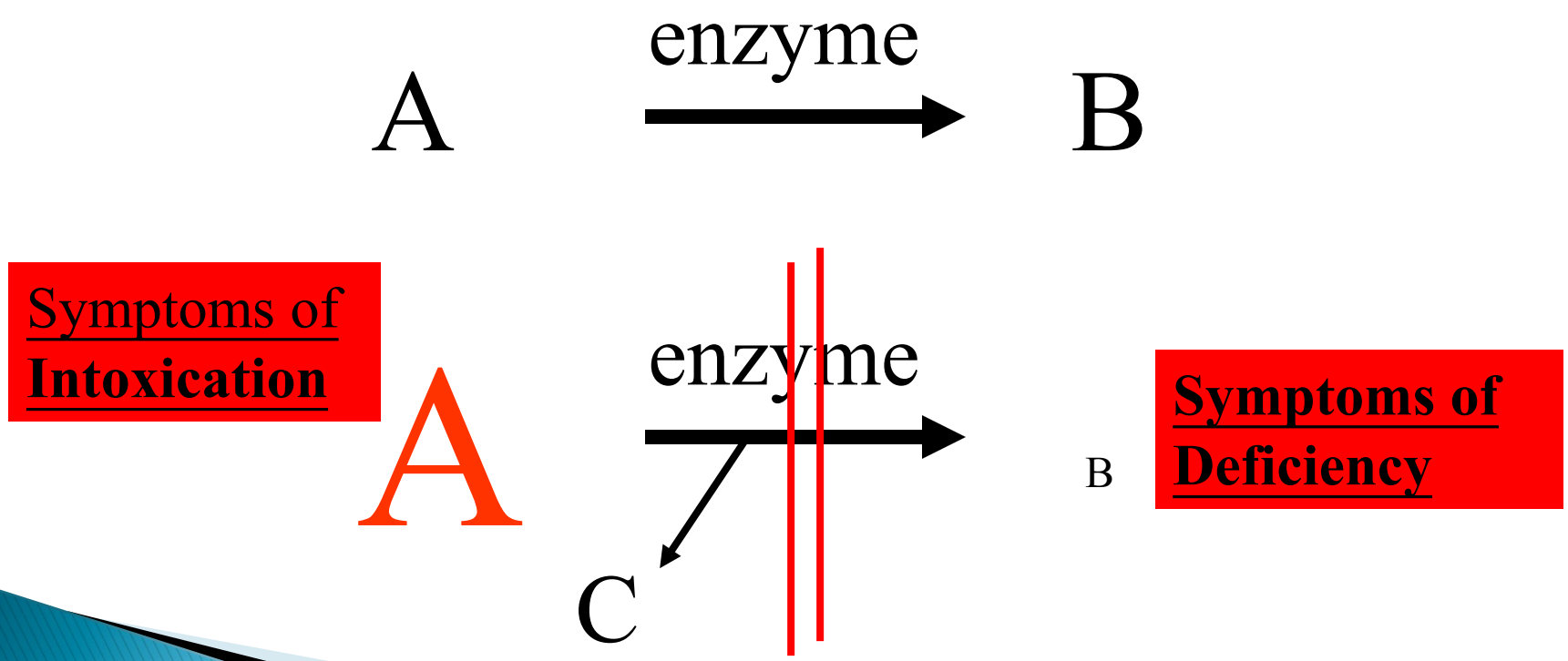
Enzyme
HAVERHILL · SUFFOLK · ENGLAND
ALACTASIA
Lactase
GANGLIOSIDOSIS GENERALIZED
β-Galactosidase
DISACCHARIDE INTOLERANCE
III Lactase
I Invertase
GALACTOKINASE DEFICIENCY
Galactokinase
GALACTOSAEMIA
Galactose-1-P-uridyl transferase
GLYCOGEN STORAGE DISEASE
I Glucose-6-phosphatase
II α-1, 4-Glucosidase
III Amylo-1, 6-glucosidase
IV Amylo-(1, 4 to 1, 6)-transglucosidase
V Muscle phosphorylase
VI Liver phosphorylase
VII Muscle phosphofructokinase
VIII Liver phosphorylase kinase
PENTOSURIA
L-Xylulose reductase
G6PD DEFICIENCY (FAVISM)
Glucose-6-P dehydrogenase
FRUCTOSURIA
Hepatic fructokinase
FRUCTOSE INTOLERANCE
Fructose-1-P aldolase
HYPEROXALURIA
D-Glyceric dehydrogenase
HYPERSARCOSINAEMIA
Sarcosine dehydrogenase
HAEMOLYTIC ANAEMIA
I Adenosine triphosphatase
II Diphosphoglycerate mutase
III Glucose-6-P dehydrogenase
V Glutathione reductase
VI Hexokinase
VII Pyruvate kinase
VIII Triosephosphate isomerase
IX Hexosephosphate isomerase
X Phosphoglycerate kinase
LIPASE DEFICIENCY (CONGENITAL)
Lipase pancreatic
LACTIC ACIDOSIS
Pyruvate dehydrogenase
β-KETOTHIOLASE DEFICIENCY
β-Ketothiolase
LEIGH'S NECROTIZING ENCEPHALOMYELOPATHY
Pyruvate carboxylase
KRABBE'S DISEASE
Galactose-ceramide hydrolase
GAUCHER'S DISEASE
Glucosyl-ceremide hydrolase
NIEMANN-PICK DISEASE
Sphingomyelinase
PYRIDOXINE RESPONSIVE ANAEMIA
α-Aminolevulinic acid synthetase
PORPHYRIA
Uroporphyrinogen synthetase
HYPERSEROTONINAEMIA
5-Hydroxytryptophan decarboxylase
TRYPTOPHANAEMIA
Tryptophan pyrrolase or formylase
XANTHURENIC ACIDURIA
Kynureninase
ALKAPTONURIA
Homogentisic acid oxidase
ALBINISM
Tyrosinase
TYROSINAEMIA
II Tyrosine transaminase
I Para-hydroxyphenyl-pyruvate oxidase
PHENYLKETONURIA
Phenylalanine hydroxylase
XANTHINURIA
Xanthine oxidase
LESCH-NYHAN SYNDROME
Hypoxanthine-guanine phosphoribosyl transferase
HYPER-β-ALANINAEMIA
β-Alanine-α-ketoglutarate transaminase
OROTIC ACIDURIA
Orotidylic pyrophosphorylase and orotidylic decarboxylase
β-AMINOISOBUTYRIC ACIDURIA
β-Aminoisobutyrate transaminase
SULPHITE OXIDASE DEFICIENCY
Sulphite oxidase
HYPERFOLICACIDAEMIA
HOMOCYSTINURIA
Cystathionine synthetase
HISTIDINAEMIA
Histidinase
CYSTATHIONINURIA
Cystathionase
HYPERMETHIONINAEMIA
Methionine-adenosyl transferase
HYPERGLYCINAEMIA (KETOTIC) PROPIONIC ACIDAEMIA
Propionyl-CoA carboxylase
HYPERVALINAEMIA
Valine transaminase
MAPLE SUGAR URINE
Keto acid decarboxylase
β-METHYL CROTONIC ACIDURIA
Methyl crotonyl-CoA carboxylase
METHYLMALONIC ACIDURIA
I Methylmalonic CoA carboxymutase
II 5' Deoxyadenosyl cobalamin synthetase
ISOVALERIC ACIDAEMIA
Isovaleric acid CoA dehydrogenase
GLUTAMIC ACIDURIA
(Cerebral Degeneration)
α-OXOADIPIC ACIDURIA
α-Oxoadipic dehydrogenase
SACCHAROPINURIA
Saccharopine dehydrogenase
HYPERLYSINAEMIA
Lysine-ketoglutarate reductase
HYPERPROLINAEMIA
I Proline oxidase
II α-1-Pyroline-5-carboxylate dehydrogenase
HYDROXYPROLINAEMIA
Hydroxyproline oxidase
CARBAMOYLPHOSPHATE SYNTHASE DEFICIENCY
CITRULLINAEMIA
Argininosuccinic acid synthetase
ORNITHINAEMIA
Ornithine transcarbamylase
HYPERORNITHINAEMIA
Ornithine-ketoacid transaminase (?)
ARGININOSUCCINIC ACIDURIA
Argininosuccinase
ARGININAEMIA
Arginase
GLUCOSE
Glucose-1-P
Glucose-6-P
Fructose-6-P
Fructose-1,6-di-P
Dihydroxy acetone-P
Glyceraldehyde-3-P
1:3-di-P-Glycerate
3-P-Glycerate
2-P-Glycerate
P-enolpyruvate
PYRUVATE
ACETYL-CoA
ACYL-CoA
ACETATE
ETHANOL
LACTATE
ALANINE
CITRATE
Cis-ACONITATE
ISOCITRATE
OXALOACETATE
MALATE
FUMARATE
SUCCINATE
SUCCINYL CoA
α-OXOGLUTARATE
ASPARTATE
GLUTAMATE
NADH
FPH
NADP
NAD
ATP
GLYCINE
SERINE
TRYPTOPHAN
TYROSINE
PHENYLALANINE
HISTIDINE
CYSTINE
METHIONINE
THREONINE
ISOLEUCINE
VALINE
LEUCINE
LYSINE
PROLINE
HYDROXYPROLINE
ORNITHINE
CITRULLINE
ARGININE
UREA
DNA
RNA
PHOTOSYNTHESIS
CHOLESTEROL
KETONE BODIES

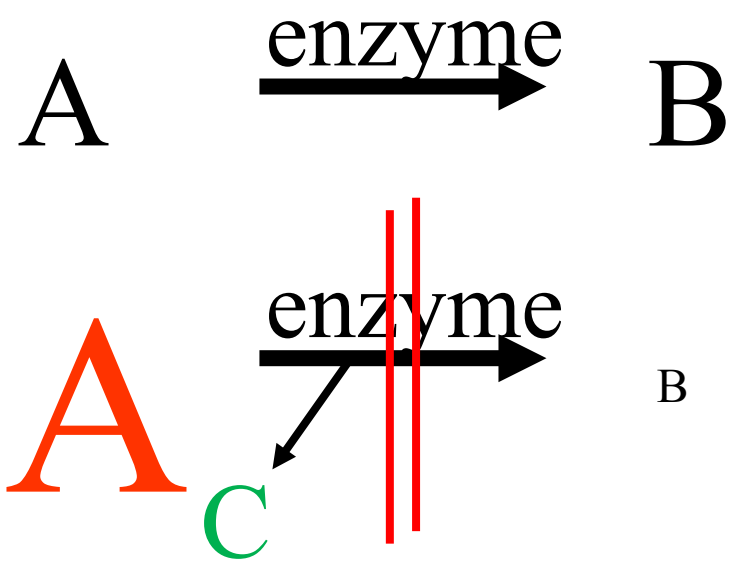
Inborn errors of metabolism (IEM)

- Defect in a metabolic pathway



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

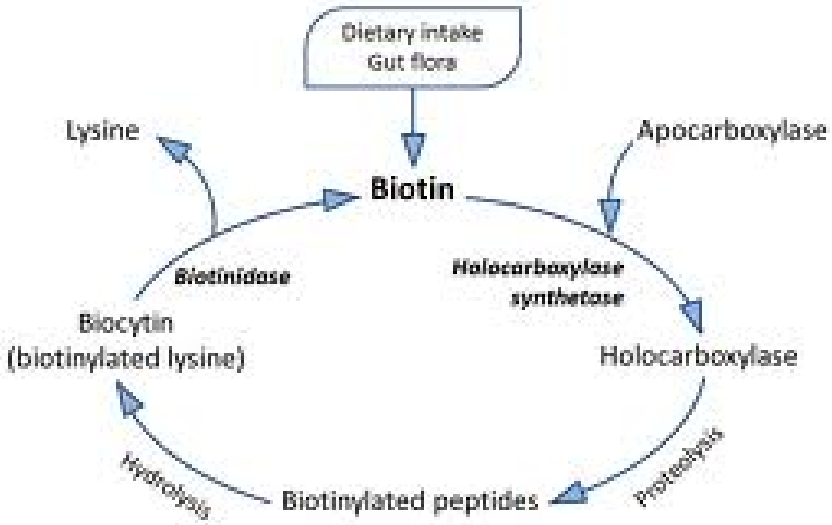


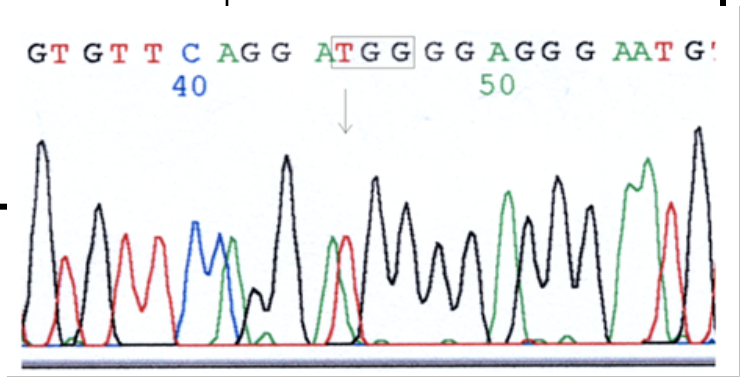
Some IEMs are easily treated with simple measures like drugs, dietary manipulation

Scaly skin rash 鱗屑疹

Holocarboxylase Synthetase deficiency
合成酶缺乏症

Age of onset	Presenting symptoms	Investigations (urine)	Confirmatory tests
• 1y	• generalised erythematous scaly skin eruption (guttae psoriasis) • episodic metabolic acidosis	• ↑ lactate • 3OH isovalerate • 3 methyl-crotonyl-glycine • 3 OH propionate (multiple carboxylase deficiency)	• defective activity of holo-carboxylase synthetase (cultured fibroblasts) • molecular genetic

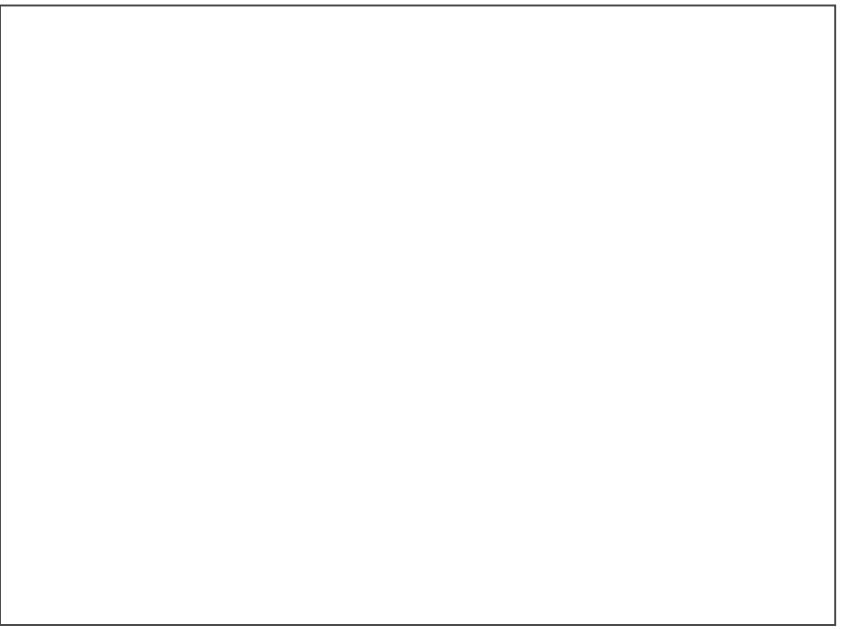


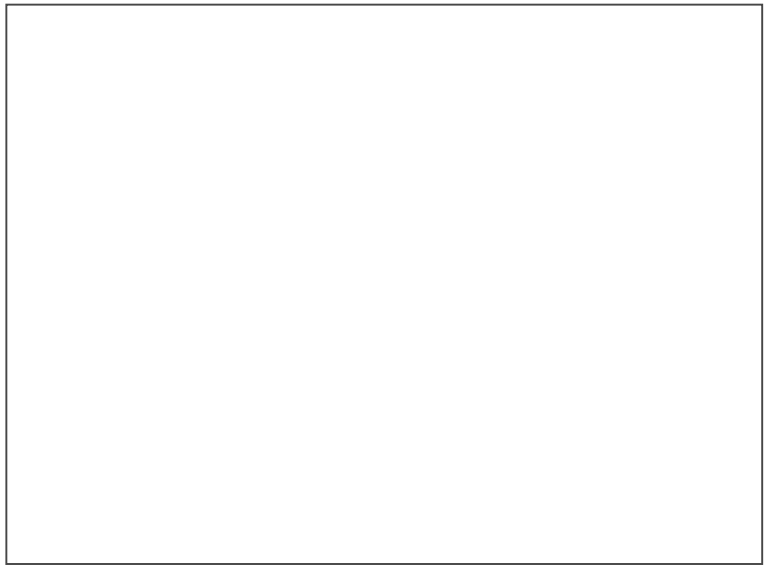


Holo-carboxylase Synthetase deficiency
合成酶缺乏症

Diagnosis	Treatment	Current Status
Multiple carboxylase deficiency (Holocarboxylase synthetase deficiency)	◆ biotin	◆ normal growth & development ◆ no further skin eruptions

Holocarboxylase Synthetase deficiency
合成酶缺乏症



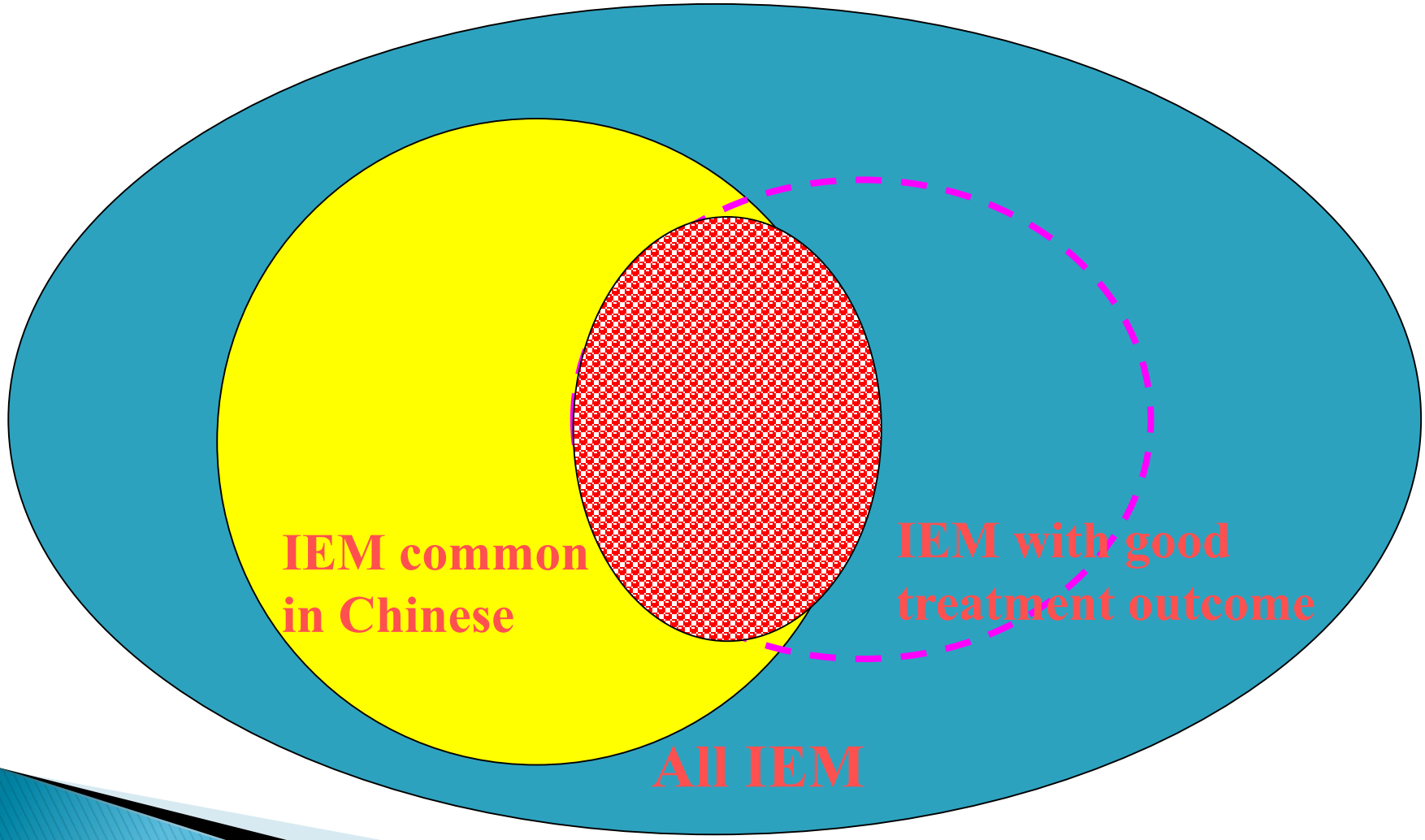


Parents as well as Doctors' wish

- 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

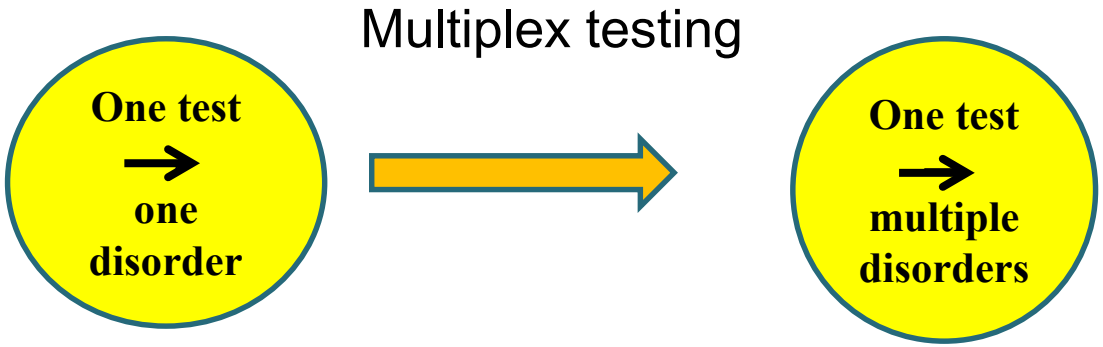
Expansion of Newborn screening –

screen for over 30 different IEMs in the newborn period

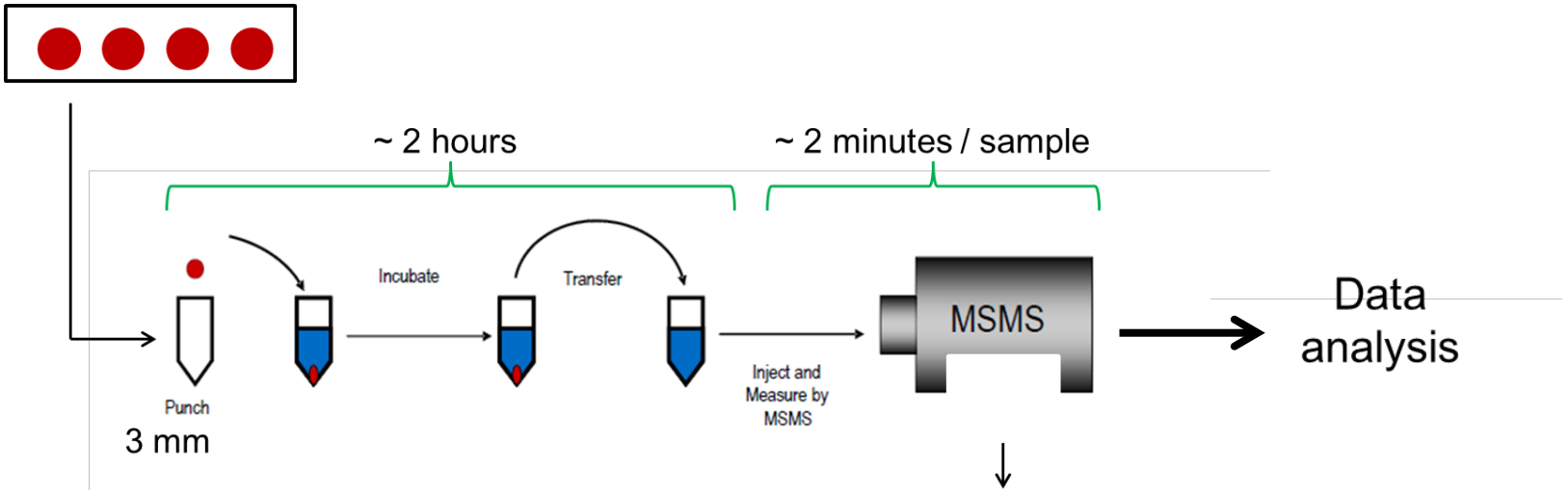
Tandem mass spectrometry (MS/MS)

revolutionized newborn screening

Tandem Mass Spectrometry (MS/MS)



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



NEWS • HONG KONG • HEALTH

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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UPDATED : Monday, 09 March, 2015, 6:02pm

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

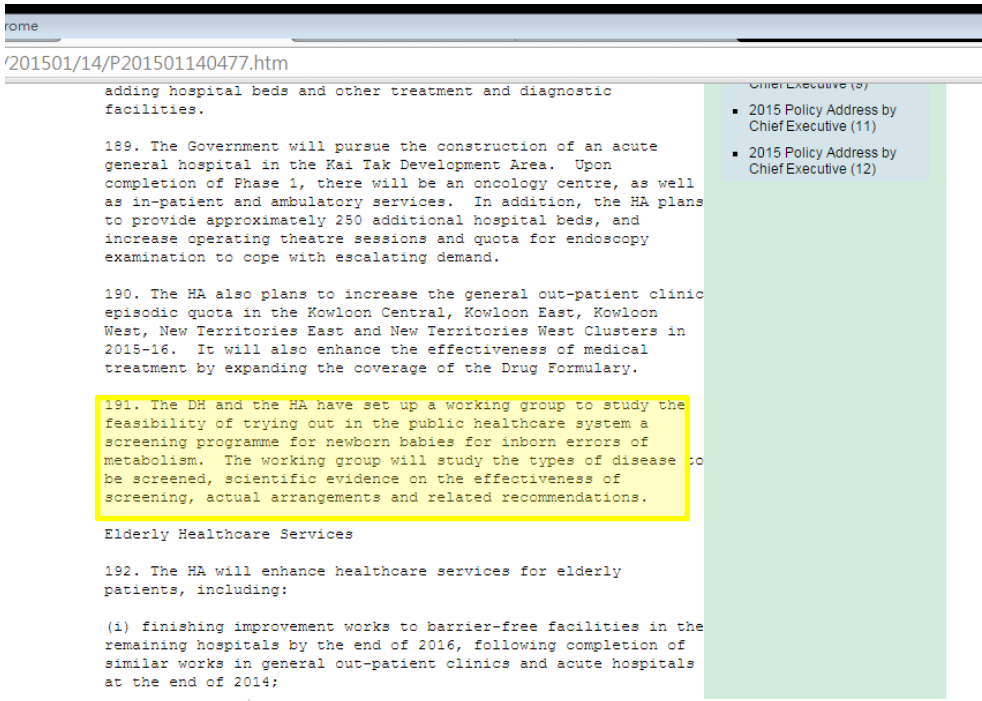
A new screening programme for newborn babies announced in the policy address is likely to involve a blood test for 12 types of inborn metabolic diseases that affect one in every 3,000 local infants, the *South China Morning Post* has learned.

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.

Chief Executive Policy Address 2015
行政長官施政報告



rome

/201501/14/P201501140477.htm

adding hospital beds and other treatment and diagnostic facilities.

189. The Government will pursue the construction of an acute general hospital in the Kai Tak Development Area. Upon completion of Phase 1, there will be an oncology centre, as well as in-patient and ambulatory services. In addition, the HA plans to provide approximately 250 additional hospital beds, and increase operating theatre sessions and quota for endoscopy examination to cope with escalating demand.

190. The HA also plans to increase the general out-patient clinic episodic quota in the Kowloon Central, Kowloon East, Kowloon West, New Territories East and New Territories West Clusters in 2015-16. It will also enhance the effectiveness of medical treatment by expanding the coverage of the Drug Formulary.

191. The DH and the HA have set up a working group to study the feasibility of trying out in the public healthcare system a screening programme for newborn babies for inborn errors of metabolism. The working group will study the types of disease to be screened, scientific evidence on the effectiveness of screening, actual arrangements and related recommendations.

Elderly Healthcare Services

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

(i) finishing improvement works to barrier-free facilities in the remaining hospitals by the end of 2016, following completion of similar works in general out-patient clinics and acute hospitals at the end of 2014;

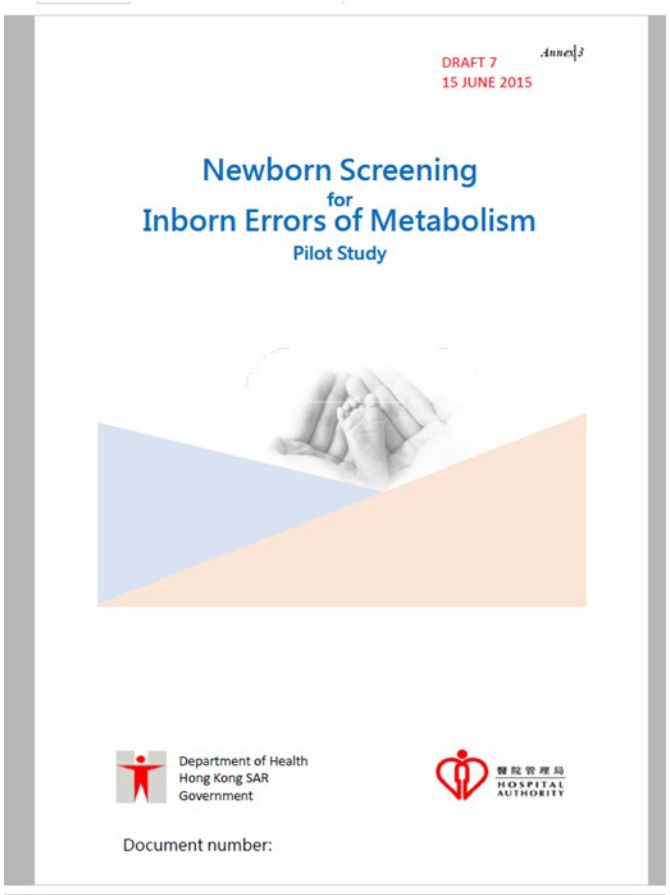
- 2015 Policy Address by Chief Executive (11)
- 2015 Policy Address by Chief Executive (12)

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



	Screened Conditions with Metabolic newborn screening programme	Drug treatment	Special milk formulae
1	Multiple carboxylase deficiency	yes (biotin)	N
2	Glutaric acidaemia type I (GAI)	Yes (carnitine, riboflavin)	Y
3	Methylmalonic acidaemia (MMA)	Yes (carnitine, hydroxycobalamin)	Y
4	Propionic acidaemia (PA)	Yes (carnitine, biotin)	Y
5	Isovleric acidemia (IVA)	Yes (carnitine, glycine)	Y
6	3-hydroxy-3methylglutaryl-CoA (HMG-CoA) lyase deficiency		N
7	Beta-ketothiolase deficiency/2-methylacetoacetyl-CoA thiolase (MAT) deficiency		N
8	Classic phenylketonuria (PKU)	Yes (BH4)	Y
9	6-pyruvoyl-tetrahydropterin synthase deficiency	Yes (BH4, sinemet, oxytriptan)	Y
10	Argininosuccinic acidaemia	Yes (benzoate, arginine)	N
11	Maple syrup urine disease (MSUD)	Yes (thiamine)	Y
12	Citrullinaemia tupe I	Yes (benzoate, arginine)	N
13	Citrullinaemia type II (Citrin deficiency)		Y
14	Tyrosinaemia type I **	Yes (nitisinone)	Y
15	Homocvstinuria **	Yes(pyridoxine, folinic acid)	Y
16	Carnitine uptake deficiency	Yes (carnitine)	N
17	Carnitine-acylcarnitine translocase deficiency (CACT)	Yes (carnitine)	Y
18	Carnitine palmitoyltransferase II deficiency (CPTII)		Y
19	Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)		N
20	Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)		Y
21	Glutaric acidaemia type II (GAII)/Multiple acyl-CoA dehydrogenase deficiency (MADD)	Yes (riboflavin, carnitine)	Y
22	Congenital adrenal hyperplasia	Yes (hydrocortisone, fludrocortisone)	N
23	Biotinidase deficiency	Yes (biotin)	N
24	Classic Galactosaemia		N
	Subtotal	**17/24**	**14/24**

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)

Pilot
(Phase 1)

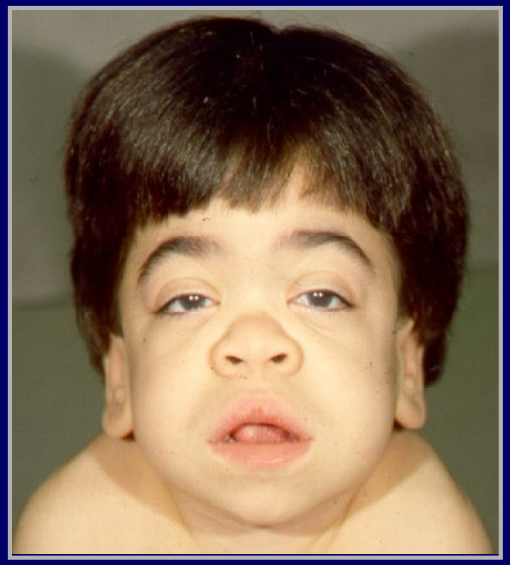
Pilot
(Phase 2)

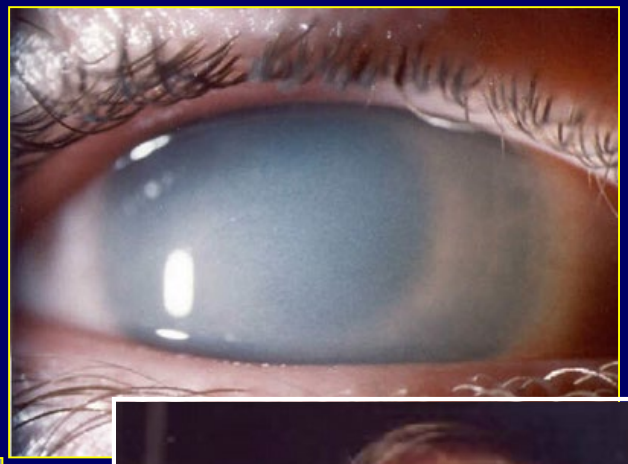
Extension into territory wide program in phases

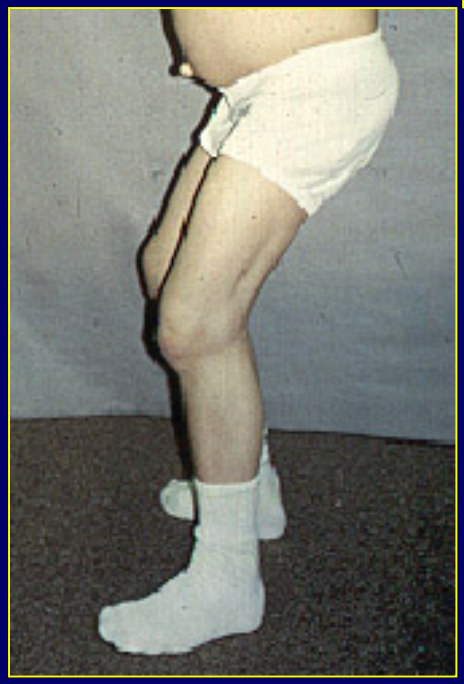
HA Hospitals	QMH QEH	QMH QEH	PWH TMH KWH	PMH PYNEH UCH
Newborns	Term	All (including preterm & sick term infants)		
No. of IEM	21	24		26
% of live births covered (HA)	< 25%	25%	70%	100%

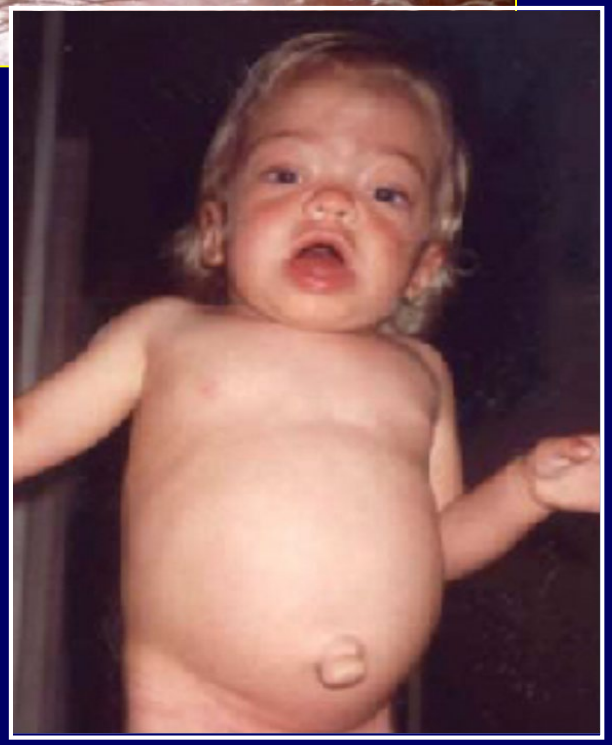
Some IEMs can be treated by more complicated measures like Transplant or Enzyme replacement therapy

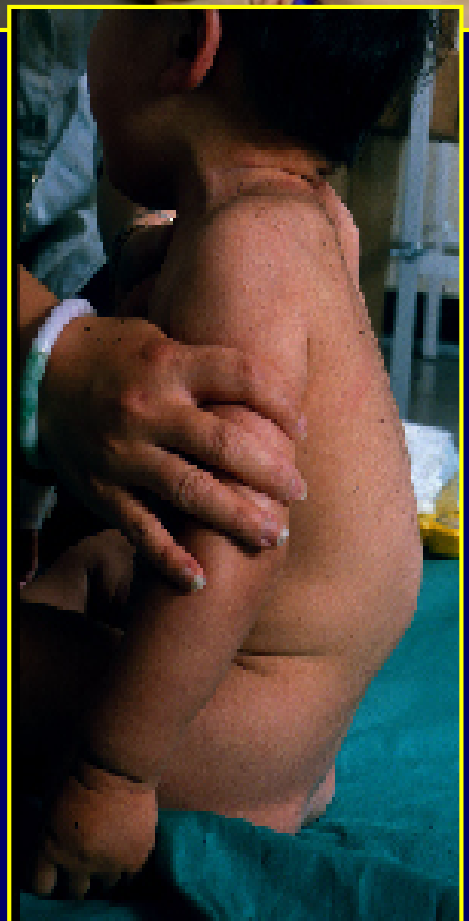
Mucopolyssacharidosis





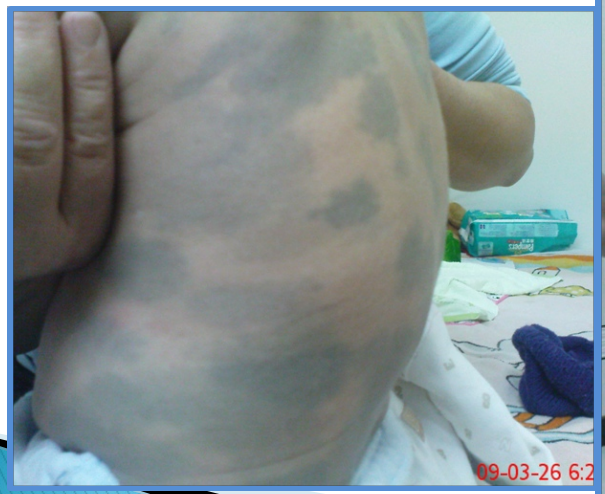


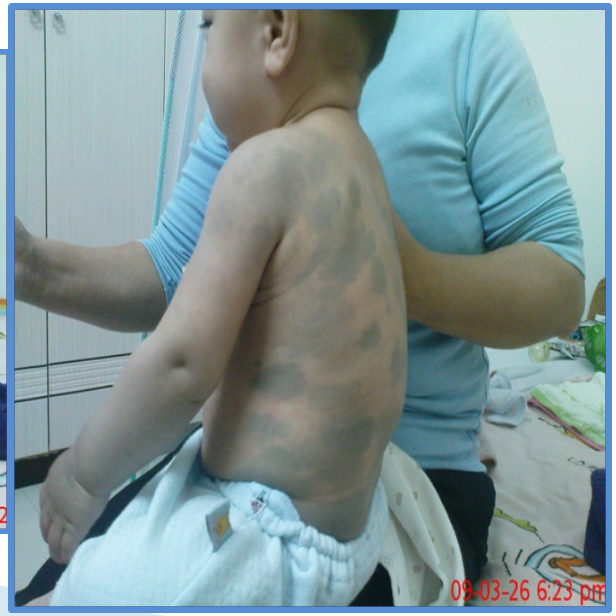




Mucopolyssacharidosis type I (Hurler syndrome)

- presented with hump over back (lumbar gibbus)
- extensive mongolian spots
- bilateral inguinal hernia





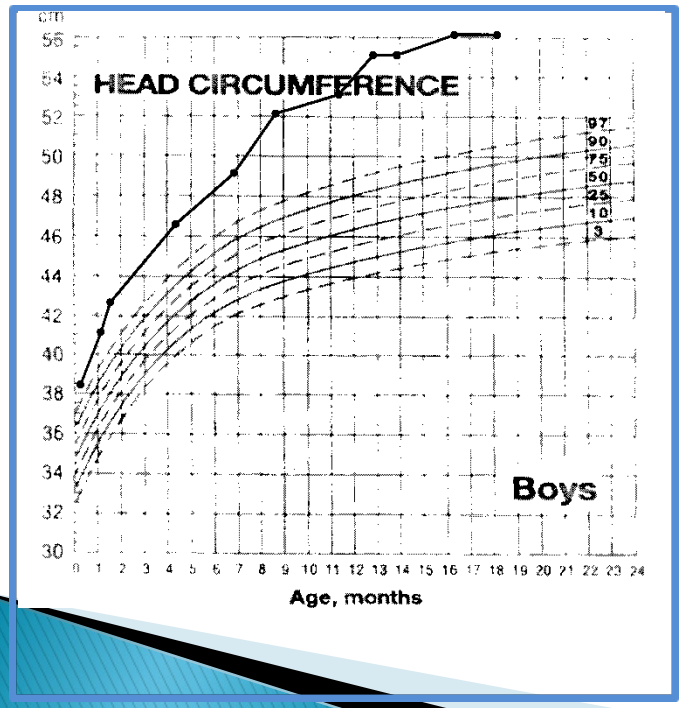
Mucopolyssacharidosis type I (Hurler Scheie syndrome)

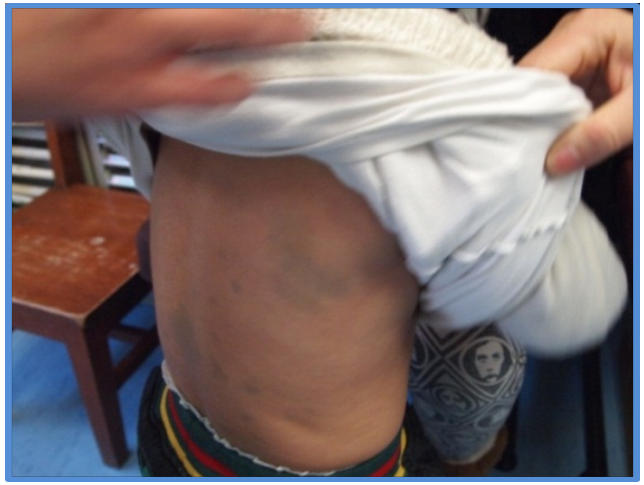
- multiple joint contractures noted since birth
- developmental delay
- severe hearing loss
- coarse facial features

- sustained cervical cord injury with C1/2 subluxation after accidental fall
- internal fixation with bone graft and external halo jacket

Mucopolyssacharidosis type II (Hunter syndrome)

- presented with big head and developmental delay
- inguinal hernia





Mucopolyssacharidosis type III (Sanfilippo disease)

- normal up until 6 y
- first presented with behavioural problems, aggressive behaviour & violance 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

Ophthalmologist

Surgeon

Pulmonologist

Interventional Geneticist

Otorhinolaryngologist

Cardiologist

Orthopedist

Neurologist

Anesthesiologist

Dentist

Gastroenterologist

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

- MPS I
- HSCT at 2y9m

- MPS VI
- HSCT at 14m

MPS VI
HSCT at 5y

Post transplant MPS patients

ENZYME REPLACEMENT THERAPY (ERT)
酵素替代疗法

- 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

香港黏多醣症暨罕有遺傳病互助小組

Hong Kong Mucopolysaccharidoses & Rare Genetic Diseases Mutual Aid Group

- 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 ~ 1in 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

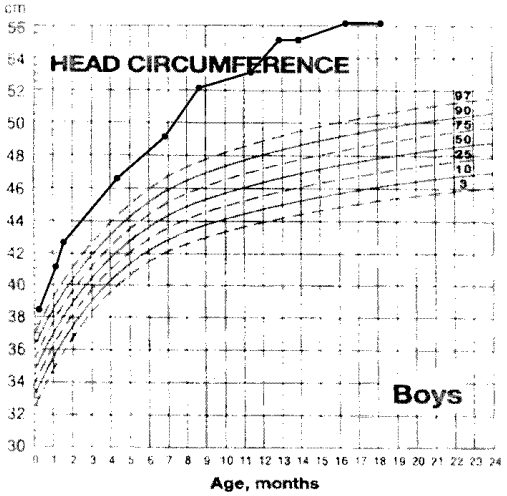
- In the exciting new era of treatment for various IEM
- Simple measures: drugs, diet
- Complicated measures : Hematopoietic stem cell transplant, Enzyme replacement therapy
- Early diagnosis & treatment are keys to treatment success
- Newborn screening has been life saving for some
- On going research 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

Mucopolyssacharidosis type III (Sanfilippo disease)

- normal up until 6 y
- first presented with behavioural problems, aggressive behaviour & violance 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

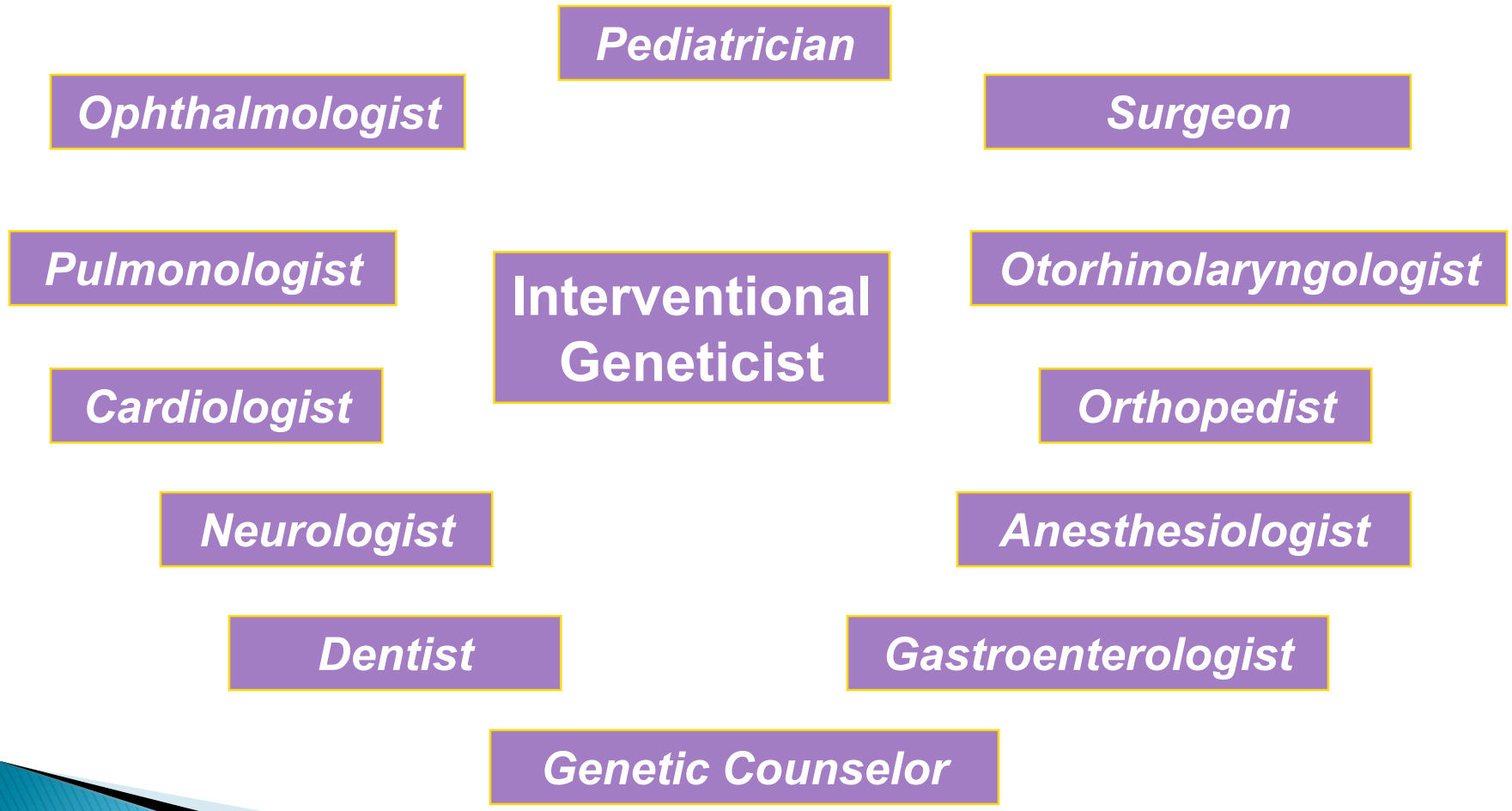
- With relative lack of other extra CNS manifestations, patients can survive into adulthood 30-40y age

- 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



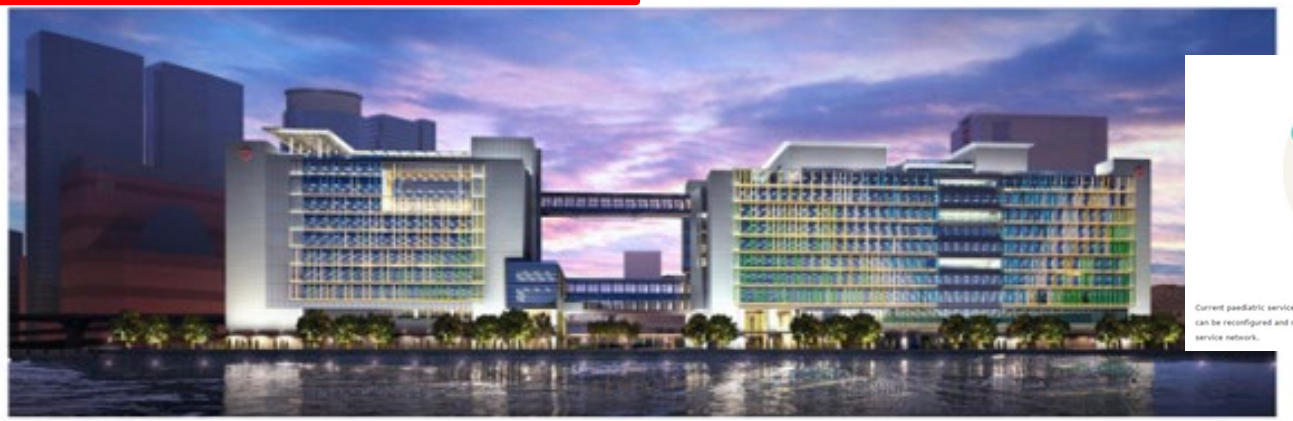
IEM patients & HKCH

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