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The Cover Shot



The picture was taken at the top of a hill in a village, Hetian at Xinjiang, China (新疆和田). It was in an early autumn morning with yellow leaves.



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Editorial

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The medical world is witnessing an exciting era of rapid advancement in the field of Inborn errors of metabolism (IEM), also known as Inherited metabolic diseases (IMD). IEM/IMD are a large group of rare genetic diseases involving disorders of metabolism. The majority of IEM/IMD are due to single gene defects that code for enzymes which facilitate the conversion of various substrates into products.

Individuals affected by IEM often have major health problems with significant morbidity and mortality. Although each disorder is individually rare, the cumulative incidence of IEM is substantial as there are thousands of different IEM disorders. Around 1 in 5,000 live births is often quoted as the incidence figures among different populations.

Tremendous progress has taken place in the IEM field since the beginning of the past century when metabolic disorders were not well understood and could only be described clinically. With rapid development in basic science and advances in modern technology, insight into the biochemical and molecular basis of many IEM conditions are now known. More and more new IEM disorders are being described and added to the list of existing conditions. At the same time, wonderful treatment opportunities are being opened up bringing hope and future to a number of these previously deemed incurable conditions.

As the prognosis for many IEM conditions have significantly improved, it becomes increasingly important that these conditions be diagnosed at the earliest instance so available treatment can be instituted before irreversible damages or premature deaths set in. While most practising clinicians may not be actively involved in the care of IEM patients, they play an important key role in early recognition and referral of suspicious patients for further diagnostic workup.

In this issue of the Medical Diary, Dr Grace Poon presented an overview of the IEM conditions that have been diagnosed and managed here in Hong Kong. The realisation that some IEM conditions are treatable if timely diagnosis is made led to the practice of universal expanded newborn screening in most developed countries. Dr Josephine Chong discussed the major advances in expanded newborn screening and addressed the issue of how the medical profession can work together to establish a universal territory wide programme here in Hong Kong. This will be a major milestone towards improving the quality of care for our local IEM patients. Despite the availability of early presymptomatic diagnosis through expanded newborn screening, some undiagnosed IEM or previously stable IEM patients may still decompensate during acute intercurrent illness. The resulting catastrophic life threatening situation can be extremely difficult to manage and often require the support of intensive care in their acute management. Drs Jasmine Chow and Winnie Chan took us through the emergency management of suspected/ confirmed IEM during such acute decompensations.

Confirming the diagnosis of most IEM requires good teamwork with valuable input from specialised chemical pathologists and proper



use of available technology. Drs Sammy Chen and Chloe Mak presented an overview on the availability and utility of various laboratory investigative tools that are essential for the diagnostic workup as well as monitoring of various IEM.

It is increasingly recognised that some neurological conditions result from abnormal metabolism affecting primarily the nervous system. This group of neurometabolic conditions is increasingly recognised as important causes for children and even adults presenting with a wide variety of developmental as well as neurological concerns. The importance of diagnosing these conditions lies in the fact that a subgroup of them is highly treatment responsive with good neurological outcome. Dr Eric Yau's article on paediatric neurotransmitter diseases gave a comprehensive overview of this group of increasingly recognised and potentially treatable neurological disorders.

The prognosis for potentially treatable IEM depends largely on early diagnosis and prompt treatment. Expanded newborn screening is the key to early diagnosis for a number of IEM conditions. Recognising and diagnosing other IEM conditions early rely on the collaborative effort of all involved medical personnel – from recognising the many variable clinical presentation with a high index of suspicion to appropriate referrals

for comprehensive diagnostic workup and then followed by institution of specific treatment and monitoring for the patient, support and counselling to the family.

With the opening of the Hong Kong Children's Hospital in 2018, the majority of the clinical services, training and research on IEM will be centralised there. Building on the ground work of major improvements that have taken place in the last two decades, existing services will be better streamlined, consolidated and developed into an even higher quality, seamless, equitable and sustainable service. More structured training on different aspects of IEM and better supported and equipped facilities for basic as well as translational research will mean a brighter and more promising future for all IEM patients and their families.

We sincerely hope you find this issue of the Medical Diary an interesting one to read. We would like to express our sincere thanks to all the authors for their valuable contribution of the articles as well their continuous effort in promoting and improving the care for IEM patients here in Hong Kong.

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12 Dec	Supervisor's perspective	Mr. Ying-hon WONG Department Operating Manager (OR/DOT/DSC/AnaClinic/EC) United Christian Hospital
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Expanded Newborn Metabolic Screening: Working towards a mandatory screening programme in Hong Kong

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Dr Josephine SC CHONG

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2014.

Background

Expanded newborn screening (NBS) of inborn errors of metabolism (IEM) is a comprehensive programme for early detection of pre-symptomatic IEM patients and to offer them treatment and intervention as early as possible so as to reduce disease related mortality and morbidity. In the past two decades, advancement in medical technology with tandem mass spectrometry MS/MS has resulted in huge advances in expanded newborn screening. The practice of newborn screening varies widely in different parts of the world depending on individual country's public health care system, public awareness, professional education, and expertise management in the field. This article highlights the current state of development and challenges of expanded newborn screening in Hong Kong.

History of metabolic disorders testing and expanded newborn metabolic screening by tandem mass spectrometry

The term "Inborn errors of metabolism" was first described in 1902 by Archibald Garrod, who marked the cornerstone of research in chemical individuality with his article titled "The Incidence of Alkaptonuria" in the *Lancet*¹. Thereafter, "Inborn errors of metabolism" (IEM) is used to describe a class of genetic disorders with defects of metabolism which are mostly due to single gene defects resulting in defective function of particular enzymes that are essential for conversion of substrates into products. These disorders may cause accumulation of toxic intermediary metabolites or inadequate essential metabolites for the body.

The history of newborn screening started in 1960s by Robert Guthrie who used dried blood spot (DBS) filter paper cards and bacterial inhibition assay to detect abnormal level of phenylalanine metabolites in patients with phenylketonuria (PKU)². Through early diagnosis and treatment with a phenylalanine restricted diet, long term intellectual disability can be prevented in PKU patients. Different techniques including gas chromatographic (GC) analysis or high-pressure liquid chromatography (HPLC) coupled with mass spectrometry (MS) were later used to detect abnormal metabolites for the diagnosis of IEM in the

80-90s. However, these tests were too labour intensive and time consuming to be used as screening tests for multiple IEM disorders. Since the 1990s, major breakthroughs took place in newborn screening with the fast atom bombardment ionisation (FAB) tandem mass spectrometry (MS/MS) technology which was able to detect diagnostic acylcarnitine³ and later amino acid profiles⁴. There are three essential procedures that take place in the mass spectrometry: ionisation, mass analysis and detection. The ionisation step separates ions from a neutral compound metabolite followed by a mass analyser and the detector. By using two mass spectrometry analysers working in tandem fashion, the MS/MS system is able to measure the ion density and mass-to-charge ratio and analyses the amount of a given mass after the process of ionisation. This testing method completely revolutionised newborn screening as it now can measure multiple analytes of amino acids and acylcarnitines in the same setting simultaneously. FAB was later replaced by electrospray ionisation (ESI) in tandem mass spectrometry (MS/MS) technology⁵⁻⁸ offering high throughput screening using automated sample injection with a more precise and stable quantitative measurement.

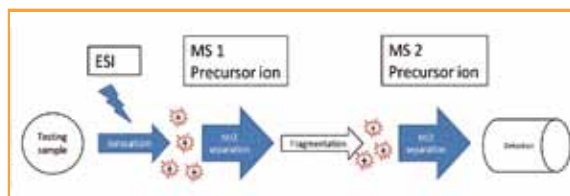


Diagram 1. Schematic flowchart of tandem mass spectrometry (MS/MS)

ESI: electrospray ionisation; MS: mass spectrometry; M/Z: mass to charge ratio

Logistics model of expanded metabolic screening programme

Expanded metabolic screening is not just offering a screening test. It should be a comprehensive programme consisting of pre-test counselling, collection of dried blood spot cards, reporting system, follow up of abnormal results, confirmation testing, treatment and management of confirmed IEM, auditing and programme evaluation. (Diagram 2)

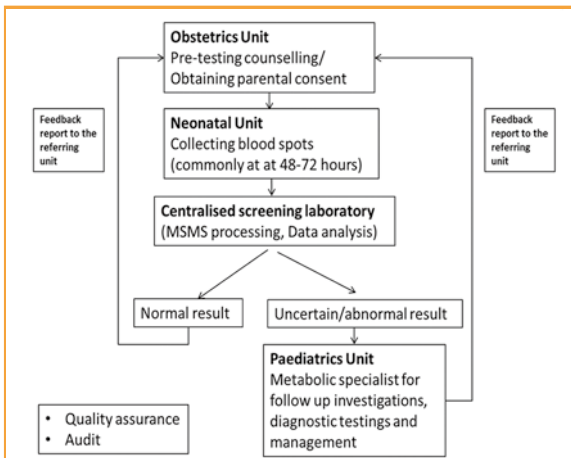


Diagram 2. Logistic model of expanded newborn screening programme
The following algorithm is a proposed model of how such a programme should be run.

Using MS/MS, the three major groups of IEM disorders that can be detected are Amino acid, Organic acid and Fatty acid oxidation disorders (Table 1).

Table 1. Examples of IEM disorders detectable with MS/MS

Inborn errors of metabolism categories	Example of target IEM disorders
Amino acid disorders	Phenylketonuria, Maple syrup urine disease, Citrullinaemia type 1, Argininosuccinic aciduria, Homocystinuria, Tyrosinaemia type 1, Arginase deficiency, Defects of bipterin cofactor biosynthesis and regeneration, Citrullinaemia type 2, Hypermethioninaemia,
Organic acid disorders	Propionic acidemia, Isovaleric acidemia, Glutaric acidemia type 1, Methylmalonic aciduria, Beta-ketothiolase deficiency, Multiple carboxylase deficiency
Fatty acid oxidation disorders	Carnitine uptake defect, Medium-chain acyl-CoA dehydrogenase deficiency, Very long-chain acyl-CoA dehydrogenase deficiency, Carnitine palmitoyltransferase I/II deficiency, Multiple acyl-CoA dehydrogenase deficiency

The sensitivity and specificity of the testing depends on the laboratory cut-off for each analyte. By using cut-offs from the worldwide collaborative project⁹, the testing can achieve a high sensitivity of above 99%. Abnormal results on repeat testings will need to be confirmed by biochemical testing with plasma amino acid, urinary organic acid analysis, enzymatic assay and/ or genetic studies. The timing of blood sampling may be different in different NBS programmes. The basic principle is to screen babies early after they have been fed for more than 24-48 hours. Delayed sampling is not suggested as early metabolic decompensation may occur in some conditions. Also, some markers like C14:1 in very-long-chain acyl-coenzyme A dehydrogenase deficiency (VLCAD) may return back to normal after several days of life giving a false negative result. Prematurity, low birth weight, neonatal jaundice, parenteral nutrition and

blood transfusions may potentially influence the results and their interpretation. Transport of samples is also important because some metabolites are unstable and degradation of blood samples may be caused by heat, humidity and transport delay. An essential component of every successful programme is the seamless logistic workflow and communication between all the involved parties. Professional as well the general public's education and awareness is an essential early integral part of any programme. Regular quality assurance and outcome evaluations become the essential subsequent key component and basis for continuation of any successful programme¹⁰⁻¹³.

Expanded newborn screening programme in other parts of the world and in Hong Kong

Tandem mass spectrometry (MS/MS) allows expansion of a panel of conditions to be added to different newborn screening programmes. Despite 50 years have passed since the first PKU screening, there are still vast differences in the practice of NBS in different countries^{14,15}. The American College of Medical Genetics adopted a uniform NBS panel since 2006 with screening for 29 cores and 25 secondary IEM conditions¹⁶. In Europe, the first pilot expanded programme was initiated in 1998 in Germany. 12 disorders are included in the current Germany panel¹⁰. UK had recently expanded the NBS panel to include six metabolic disorders¹⁷. In the Asia Pacific region, the screening of PKU was started in the 60s in Australia, New Zealand, and Japan¹⁵. The latest NBS panel in Australia is similar to the US panel including more than 20 IEM conditions¹⁸. Other Asia Pacific countries like Japan, Taiwan, Philippines, and Korea all have different expanded NBS panels^{15,19}. Shanghai is the first city in China to have expanded newborn screening since 2003²⁰. In Singapore, an expanded newborn screening programme to cover for more than 25 conditions was started in 2006 and its coverage is over 70% of the population's annual births²¹.

In Hong Kong, a newborn screening programme using cord blood to screen for Glucose-6-phosphate dehydrogenase deficiency (G6PDD) and congenital hypothyroidism was initiated in 1984 by the Clinical Genetics Service of the Department of Health. Hearing screening was added since 2007. However, there has not been any further development since and there is no universal expanded newborn screening for IEM yet in Hong Kong^{22,23}.

Incidence of Inborn errors of metabolism and a pilot expanded newborn metabolic screening programme in Hong Kong

Although the incidence of individual IEM is rare, the overall incidence of IEM is estimated to be around 1 in 4,122 to 5,000 live births by colleagues who are involved in the care of IEM patients in various Hospital Authority hospitals in Hong Kong²⁴⁻²⁶. Based on a large-scale newborn screening²⁰ covering over 17,000,000 newborns, the prevalence of IEM in China was estimated to be 1 in 5,800.



Seeing the immense need of diagnosing treatable IEM patients at the earliest instance before irreversible neurologic sequelae set in and in an effort to obtain local experience with running expanded metabolic screening here in Hong Kong, the Centre of Inborn Errors of Metabolism of The Chinese University of Hong Kong implemented a pilot voluntary participation fee-for-service expanded NBS screening programme in July 2013. The programme offers screening for 30 IEM conditions using dried blood spot filter paper card and tandem mass spectrometry (MS/MS) technology. Over the last 15 months, more than 9,000 local newborn babies were screened. The Centre received dried blood spot cards (DBS) from 12 maternity and paediatric units in Hong Kong. More than 97% of the DBS were collected within 7 days of life. 23 babies had positive results and were called back for repeat DBS +/- additional metabolic investigations. The recall rate was 0.27% (23/8,597). There were three true positive cases whose diagnoses were subsequently confirmed by biochemical and molecular genetic testing. One baby was confirmed to have Medium-chain acyl-CoA dehydrogenase deficiency (MCAD). The baby and family were immediately followed up and counselled regarding the importance of avoiding fasting. The second true positive case was confirmed to have 2-methylbutyryl-Co A dehydrogenase deficiency which is a benign condition with no active intervention necessary. Following exclusion of Homocystinuria, the third true positive case was diagnosed with Methionine adenosyltransferase deficiency, a benign condition causing hypermethioninaemia. Interestingly, two mothers were diagnosed to be carriers of metabolic conditions through the abnormal newborn screening result in their babies. One mother was found to be a carrier of Methylcrotonyl CoA carboxylase deficiency and the other mother carrier of Carnitine uptake defect. Both babies were not affected by these conditions. There were a total of 18 false positives and most of them were from a low free carnitine level. The results of over 94% of the samples were reported within a turn-around time of three calendar days. Valuable experience with logistics running and data interpretation have been gained from this pilot programme which will contribute towards the future implementation of a territory wide universal mandatory programme for all newborn babies here in Hong Kong²⁷.

Conclusion

Newborn screening (NBS) of inborn errors of metabolism (IEM) by tandem mass spectrometry (MSMS) is a world recognised cost effective public health programme aiming at reducing the morbidity and mortality associated with IEM. A territory-wide mandatory screening programme should be implemented in Hong Kong as soon as possible and without undue delay. The programme should be a multidisciplinary effort involving all the different stakeholders working together in a well-coordinated and seamless fashion covering all the following components - education, testing, and follow-up of abnormal results, confirmatory testing, diagnosis, treatment, audit, and outcome evaluation.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Expanded Newborn Metabolic Screening: Working towards a mandatory screening programme in Hong Kong" by Dr Josephine SC CHONG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2014. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

- 1. The laboratory testing method in expanded newborn metabolic screening programme is by using tandem mass spectrometry.
2. Tandem mass spectrometry method can analyse multiple analytes in one test run.
3. Without early diagnosis and treatment, patient with phenylketonuria (PKU) will be suffering from permanent intellectual disability.
4. The outcomes of all IEM disorders are the same even with early newborn screening.
5. Medium-chain acyl-coA dehydrogenase deficiency (MCAD) is an organic acid disorder.
6. The recommended timing for DBS sampling is as early as possible after the baby has been fed for 24-48 hours.
7. The dried blood spot cannot be collected by heel pricking.
8. Parental nutrition and blood transfusion may affect the newborn metabolic screening result.
9. Expanded newborn metabolic screening programme has not been started in China.
10. The expanded newborn metabolic screening is part of mandatory newborn screening programme in Hong Kong.

ANSWER SHEET FOR DECEMBER 2014

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2014 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Expanded Newborn Metabolic Screening: Working towards a mandatory screening programme in Hong Kong

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Answers to November 2014 Issue

- Managing Multi-morbidity: the Important Role of the Family Doctor
1. T 2. T 3. F 4. F 5. T 6. T 7. F 8. T 9. F 10. T

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Overview of Inborn Errors of Metabolism in Hong Kong

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Dr Grace WK POON

Inborn errors of metabolism (IEM) are often regarded as uncommon problems in medical practice and are relatively unfamiliar to primary care physicians. Although individually rare, IEM are collectively quite common. The estimated birth prevalence ranges from 1 in 784 to 1 in 2,555.¹⁻³ In 2011, Lee HC et al. reported that the incidence of IEM in Hong Kong was estimated to be 1 in 4,122 live births.⁴ Considering the population of Hong Kong was 7.19 million and there were 57,100 live births in 2013, it would imply that there were an estimated 2,814 to 9,170 patients and 14 new cases with IEM in Hong Kong. IEM has frequently been thought of as a group of rare inherited metabolic disorders involving numerous complicated biochemical pathways and metabolites, with variable presentations from nonspecific clinical symptoms to acute life-threatening events with fatal outcomes. In fact, extensive understanding of the biochemical pathways and individual metabolic disorders is NOT required to save a life; rather it is the high index of suspicion that is most critical for early identification of these disorders. A basic understanding of the distinct characteristics and clinical manifestations of different types of IEM provides the basis for preliminary diagnosis. Early treatment can stabilise or even reverse the acute symptoms preventing chronic disability. The many new technologies in the field of biochemical and genetics testing are now available in Hong Kong and we are able to diagnose many IEM with tests performed locally. Accurate diagnosis of IEM also plays a major role in family planning, genetic counselling and prenatal diagnosis. More importantly, the treatment efficacy for IEM has improved significantly over the years. It was reported that only 12% of IEM had fully responded to treatment in 1983, but by 2008 more than 30% of IEM had a full response to treatment.⁵ We now have many more new treatment modalities for managing patients with IEM such as enzyme replacement therapy and organ transplantation.

Newborn babies can now be screened for certain serious but treatable IEM by using a SINGLE test with tandem mass spectrometry to analyse acylcarnitines and amino acids from a simple dried blood spot sample, so that timely treatment can be started in those affected babies in the pre-symptomatic phase to prevent acute catastrophic event and chronic irreversible damage. Expanded newborn screening (NBS) to include IEM is fast becoming the gold standard worldwide, and it should be the way forward in Hong Kong. Currently expanded NBS for IEM is only being offered to babies born in the private sector in Hong Kong but screening for the entire population should be the ultimate goal. The panel of disorders to be included in our expanded

NBS programme needs to be further discussed since it appears that our local disease pattern may be different from that in the Western societies. Even though there may be ample benefits from performing expanded NBS for IEM, there may also be risks applied both to the babies being tested and to the family, including parental anxiety, stigmatisation, and possible exposure to discrimination. These are some important issues that have to be considered before embarking on expanded NBS for IEM in Hong Kong.

The Clinical IEM Service in Hong Kong

Chau ASH et al. first reported 3 Chinese children with glycogen storage disease, Gaucher disease and galactosaemia respectively in Hong Kong in 1966.⁶ Since then, there have been many more publications of local Chinese patients with IEM. These patients were often managed in different medical or paediatric units of regional public hospitals. As each unit probably only managed a few new cases of IEM a year, the expertise in the area has been very scattered. Many IEM patients may have gone undiagnosed due to the less than straightforward diagnostic process. The Clinical Genetic Service of the Department of Health has also played a major role in the management of these patients for genetic diagnosis and counselling. The Department of Paediatrics at the Prince of Wales Hospital of The Chinese University of Hong Kong was the first to establish a Joint Metabolic Clinic in 1997, run by paediatricians, chemical pathologists and dietitians, providing a comprehensive and multidisciplinary care to patients with IEM. Since then, similar joint metabolic clinics have been established in other regional hospitals in Hong Kong namely the Princess Margaret Hospital since 2002, the Queen Mary Hospital since 2003 and the Queen Elizabeth Hospital since 2009. Together with Prince of Wales Hospitals, these four hospitals were later established as specialist centers for treating lysosomal storage disorders with enzyme replacement therapy.

Hong Kong Society of Inborn Errors of Metabolism

The first "Conference on Inborn Errors of Metabolism in Infants and Children: Hong Kong 2002" was jointly organised by six professional societies on 4-6 October 2002.⁷ There were 220 IEM cases registered in the Hong Kong Paediatric Metabolic Registry at the time (Table 1). The Hong Kong Society of Inborn Errors of Metabolism



(HKSIEM), a member of the Federation of Medical Societies of Hong Kong, was subsequently formed in 2004 by a group of clinicians including paediatricians, geneticists, obstetricians, chemical pathologists, dietitians and other allied health professionals, together with scientific officers in the biochemical and genetic laboratories. Some of the main objectives of the HKSIEM include the promotion of the study and management of patients with IEM and to establish a local IEM registry. Since its inception, the HKSIEM has organised regular clinical meetings and annual training courses, networking with other organisations and collaborating with a local patient support group, the Hong Kong Mucopolysaccharidoses & Rare Genetic Diseases Mutual Aid Group (mps.org.hk).

The Hong Kong IEM Registry and our local disease pattern

A retrospective study on all patients less than 19 years of age on first consultation, with a metabolic diagnosis (ICD-9 codes) that were managed in the paediatric units under the Hospital Authority of Hong Kong from 1 July 1999 to 30 June 2009 was conducted. The data were taken from CDARS, CMS, metabolic clinic log and the individual hospital unit's database of paediatric patients. There were 486 patients included in the study. Each patient was classified using the Society of the Study of Inborn Errors of Metabolism (SSIEM) classification of inborn errors of metabolism. As listed in Table 2, the 486 patients were classified into 14 different groups of IEM. The largest group of IEM patients had disorders of amino acid and peptide metabolism such as urea cycle disorders and organic acidurias (22%), followed by lysosomal storage disorders such as mucopolysaccharidosis (14%) and disorders of energy metabolism such as mitochondrial respiratory chain disorders (12%). What is interesting in our cohort is that we seem to see a different spectrum of IEM in our patients when compared to IEM that are more commonly seen in the Western societies.

Here are some interesting IEM cases that we have managed in Hong Kong:

1. Compared with the Western societies, we see less of the classical phenylketonuria in our cohort (n=2) but instead our patients with hyperphenylalaninaemia have a form of disorders of pterin metabolism namely 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency (n=11). PTPS is involved in the biosynthesis of tetrahydrobiopterin (BH₄), which is a cofactor for phenylalanine hydroxylase, the enzyme involved in phenylalanine catabolism. Children with PTPS deficiency often present within the first year of life with developmental delay, dystonia and possible seizures but they can easily be treated with oral administration of BH₄ and precursors of CNS neurotransmitters.
2. Similarly we see more patients with citrin deficiency than the other types of urea cycle defects (36 out of 58 cases of urea cycle defects). These patients were often suspected to have biliary atresia as they present in the neonatal period with prolonged jaundice and intrahepatic cholestasis. Generally the symptoms are not severe. These babies can usually be managed by dietary treatment and the symptoms often resolve by one year of age.
3. The commonest type of organic acidurias seen in our locality is glutaric aciduria type 1 (10 out of 31 cases of organic acidurias) which is an autosomal recessive disorder of lysine and tryptophan metabolism caused by deficiency of glutaryl-CoA dehydrogenase. Affected children often present with macrocephaly, followed by acute encephalopathic crisis precipitated by catabolic stress and resulting in irreversible brain injury. Sometimes they can be mistaken for the shaken baby syndrome as they could have intraretinal haemorrhages on examination and chronic subdural effusions in addition to the classic fronto-temporal atrophy on MRI brain. Treatment includes dietary therapy and strict adherence to an emergency protocol during acute stress.

Table 1. The Hong Kong Metabolic Registry 1982-2002, presented in the "Conference on Inborn Errors of Metabolism in Infants and Children: Hong Kong 2012" on 4-6 October 2002.

Types of inborn errors of metabolism	Number of patients
Lysosomal storage disease	41 (19%)
Organic acidemia	34 (16%)
Carbohydrate metabolic disorder	31 (14%)
Mitochondrial disease	27 (12%)
Amino acid disorder	20 (9%)
Cholesterol and lipid disorder	18 (8%)
Fatty acid oxidation disorder	18 (8%)
Urea cycle disorder	17 (8%)
Peroxisomal disorder	11 (5%)
Disorder of mineral metabolism	3 (1%)
Total	220 (100%)

Table 2. The Hong Kong IEM Registry. The data were presented in the Clinical Genetics Symposium Series S1 – Inborn Errors of Metabolism, jointly organised by HKSIEM, Department of Obstetrics and Gynaecology and Department of Paediatrics of the Prince of Wales Hospital, The Chinese University of Hong Kong on 12 January 2013.

Types of inborn errors of metabolism	Number of patients
Disorders of amino acid and peptide metabolism	109 (22%)
Lysosomal storage disorders (excluding Pompe disease)	69 (14%)
Disorders of energy metabolism	59 (12%)
Disorders of carbohydrate metabolism (including Pompe disease)	54 (11%)
Disorders in the metabolism of trace elements and metals	45 (9%)
Disorders of lipids and lipoprotein metabolism	37 (8%)
Disorders in the metabolism of vitamins and cofactors	35 (7%)
Disorders of fatty acid and ketone body metabolism	26 (6%)
Peroxisomal disorders	22 (5%)
Disorders of neurotransmitter metabolism	17 (3.4%)
Disorders of the metabolism of sterols	5 (1%)
Disorders in the metabolism of purines, pyrimidines and nucleotides	4 (0.8%)
Congenital disorders of glycosylation	3 (0.6%)
Disorders in the metabolism of xenobiotics	1 (0.2%)
Total	486 (100%)

4. For the fatty acid oxidation defects, we have more patients with the more severe form of carnitine acylcarnitine translocase (CACT) deficiency (n=9) than the commonly seen medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (n=1 in our cohort) in the Western societies. We have seen a few cases of carnitine uptake defect (n=5). These children are usually asymptomatic but often present with an acute metabolic crisis with poor feeding, vomiting, irritability, lethargy, hypoketotic hypoglycaemia, hepatomegaly, liver derangement and hyperammonaemia, simply triggered by fasting or common illnesses such as gastroenteritis or an upper respiratory tract infection. It is important to diagnose these patients early as the myopathy involving the heart and skeletal muscles can be easily managed with administration of levocarnitine before irreversible organ damage occurs.
5. For disorders in the metabolism of vitamins, cofactors, early diagnosis of the deficiency and timely supplementation of vitamin or cofactor in the affected patient is usually highly effective in reversing the abnormalities even though there may be some variability in response, such as oral biotin in the case of biotinidase deficiency (n=2) and holocarboxylase synthase deficiency (n=7).
6. For disorders in the metabolism of trace elements and metals, such as Wilson disease (n=43), a disorder of copper metabolism in which copper excretion from the liver is reduced, resulting in progressive accumulation of copper in the liver and other organs including the brain, kidneys and the eyes, treatment is directed towards reducing the amount of copper in the body by dietary control and chelation therapy.
7. Lastly, we have a relatively large proportion of patients in our cohort with lysosomal storage disorders (LSD, n=76 including 7 Pompe patients that were classified under disorders of carbohydrate metabolism using the SSIEM classification) and the biggest group of patients in this category has mucopolysaccharidosis (MPS, 41 out of 76 patients with LSD). Mucopolysaccharidosis is a group of rare inherited metabolic disorders in which a lysosomal enzyme is missing or insufficient, resulting in excessive build-up of long chains of sugar carbohydrates (glycosaminoglycans) in the cells that help to build connective tissues such as bone, cartilage, corneas and skin. The disorders may not be apparent at birth but signs and symptoms develop with age as more cells get damaged. In addition to haemopoietic cell transplantation in some types of MPS, recent enzyme replacement therapy (ERT) have been shown to be effective in dealing with the symptoms of MPS I, II, IVA and VI. However ERT is very expensive and involves lifelong treatment. We now also have ERT for other types of LSDs including Gaucher disease (n=3), Fabry disease (n=1) and Pompe disease (n=7).

As illustrated in these cases, it is important to recognise the signs and symptoms of patients with IEM early as a timely referral to a metabolic specialist and early diagnosis and treatment are crucial in the management of these patients.

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Emergency management of suspected Inborn Errors of Metabolism (IEM)

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Introduction

Inborn errors of metabolism often present acutely as life-threatening conditions. As their presentations are nonspecific, a high index of suspicion is required for early treatment to reduce neurological sequelae and to prevent mortality. The emergency management of inborn errors of metabolism presenting with acute decompensation is discussed here.

Presentation

Inborn errors of metabolism may present at any time after birth. Patients may be symptom free, then present when the metabolic stress of an acute disorder exceeds the body's threshold for compensation.

Common presentations include:

- 1) Neurological symptoms: Acute encephalopathy, seizures, stroke-like illness, hypotonia, ataxia
- 2) Hypoglycaemia
- 3) Disorders of acid-base regulation
- 4) Poor feeding / sucking in neonatal period
- 5) Recurrent unexplained vomiting with severe dehydration
- 6) Acute liver dysfunction
- 7) Cardiomyopathy and cardiac arrhythmias

History

Enquire about any past history of episodic vomiting and drowsiness, which may have been precipitated by intercurrent infections or fasting. History of developmental delay and family history of affected siblings or distant relatives with metabolic disorders, undiagnosed deaths, and consanguinity may provide important cues.

Laboratory evaluation

*Critical samples should be taken at the event of decompensation

Basic metabolic investigations:

- Electrolytes, anion gap, blood gases
- Liver and renal function tests
- Creatinine kinase
- Uric acid
- Plasma glucose

- Plasma lactate
- Plasma ammonium
- Urinary ketones +/- blood for ketones
- Complete blood count
- (plus insulin, cortisol and growth hormone in hypoglycaemic patients)

Special metabolic investigations:

- Plasma amino acids
- Carnitine and acylcarnitine profile
- Urinary organic acids
- Pyruvate
- Blood sample for DNA analysis

Management

Initial management:

Principles of emergency management of acute metabolic decompensation include promoting removal of toxic intermediates/metabolites from the body with drugs or dialysis, prevention of further catabolism and promotion of anabolism. The following steps should be taken: intensive care, diagnostic investigations, nutritional restriction, toxin removal, biochemical monitoring, and additional treatments according to biochemical abnormalities and diagnosis.

Whilst waiting for investigation results, stabilisation of the patient according to ABCs should ensue. Assisted ventilation, fluid resuscitation and circulatory support may be required to ensure good tissue perfusion. Antibiotics therapy is recommended as sepsis is an important consideration in the differential diagnosis, and may be a precipitating factor for decompensation.

Patients should be kept nil per oral in order to decrease the intake of any precursors to the defective process of metabolism. Prevention of further catabolism and promotion of anabolism is of essence. Hence, patients should be treated with 10-12.5% dextrose infusion at 1.5 times of maintenance and concomitant use of insulin if anabolism is not achieved. Intravenous Frusemide may be considered to avoid fluid overload. Exception to empirical use of high-rate dextrose infusions as an initial management is the treatment of pyruvate dehydrogenase complex deficiency and mitochondrial respiratory chain disorders. Consider infusion of intralipids initially at 1g/kg/day when a fatty acid oxidation disorder has been ruled out.



Special problems:

Hypoglycaemia: Hypoglycaemia should be clearly documented with critical investigations drawn at the same time if possible. Correction of hypoglycaemia with intravenous glucose has to be provided. Identify the underlying cause allows for specific treatment.

Metabolic acidosis: Take note that peripheral perfusion, dehydration and infection should be corrected first with supportive management. Bicarbonate therapy should be considered if pH <7.1, and administered slowly at half correction. Renal replacement therapy is indicated if the acidosis is not controlled with repeated doses of bicarbonate infusion.

Hyperlactataemia: Apart from a reflection of tissue hypoxia, hyperlactataemia may indicate an underlying primary metabolic disorder. Regardless of the mechanism, severe hyperlactataemia is especially detrimental to cardiovascular stability. Using bicarbonate buffered replacement and dialysate fluid in dialysis therapy can safely and effectively bring down the toxic level of lactate.

Seizure control and cerebral oedema: Acute encephalopathy is a common presentation ranging from drowsiness, lethargy, unsteady gait to seizures. Patients may develop cerebral oedema and subsequent herniation. Hence, early recognition and intervention is essential. Sodium valproate, steroid and thiopentone should be avoided.

Hyperammonaemia: Hyperammonaemia is a metabolic emergency requiring urgent treatment to prevent irreversible brain damage. Hyperammonaemic coma occurs when the serum ammonia level is greater than 300 umol/L. Hyperammonaemia is extremely toxic to the brain per se or through intracellular excess glutamine formation, causing astrocyte swelling, brain oedema, coma and even death. Prognosis depends on the duration of coma. Hence emergency treatment should be started even before a definitive diagnosis could be made.

- Elimination of exogenous sources of nitrogen, minimisation of the production of endogenous nitrogen (high caloric intravenous infusions, non-absorbed gastrointestinal antibiotics, laxatives)
- Facilitation of the removal of waste nitrogen by water diuresis or dialysis. The patient should be kept polyuric and yet not fluid overloaded to avoid worsening of cerebral oedema.
- Nitrogen scavengers should be used if a urea cycle disorder is suspected. Intravenous sodium benzoate and sodium phenylacetate or oral sodium phenylbutyrate along with intravenous arginine are indicated.

Dialysis therapy for hyperammonaemia: Ammonia is non-osmolar so there is no risk of dialysis disequilibrium syndrome when its level is brought down abruptly. In fact, the rapidity of ammonia clearance and haemodynamic condition of the patient are the two major concerns in choosing a dialysis modality in this situation. The small molecular size of ammonia and the high clearance rate possible with diffusion-based therapy have supported haemodialysis (HD) or continuous veno-venous haemodiafiltration

(CVVHD) as the preferred methods of toxin removal. Both HD and CVVHD require special vascular access which could be difficult and even fail to obtain in the neonatal population. If no alternative is available, peritoneal dialysis should be provided as early as possible. However, it is generally unable to keep up with the ammonia generated in these metabolic disorders. With severe hyperammonaemia (> 1500 umol/L), either acute HD or high volume CVVHD at the range of 4000-6000 ml/m²/hr dialysate flow rate should be started. If acute HD is chosen as the treatment modality, continuous treatment with the usual CVVHD with dialysate and replacement fluid rate at 2000ml/m²/hr has the advantage to provide continuous removal of ammonia and avoid the rebound of ammonia in the circulation. In general, CVVHD provides a safe, efficient and haemodynamically stable clearance. For hyperammonaemia level at 200-500 umol/L, treatment with the usual CVVHD regime would be sufficient to bring down the ammonia levels in hours. Special attention to fluid balance and electrolytes disturbances is mandatory to avoid serious complications during these therapies. In general, addition of potassium chloride solution to the dialysate and replacement solutions, making a potassium concentration of 4 mmol/L fluids provides a stable and safe serum potassium level. Vigilant titration of anticoagulation therapy and secure vascular access are the mainstay for system survival. However, to avoid citrate toxicity, anticoagulation regime using citrate should be avoided in this group of patients.

Specific treatment:

Vitamin or coenzymes act as cofactors in many metabolic pathways, and can stimulate residual enzyme activity. Vitamin cocktail (Table 1) is only indicated in acutely ill patients with a clinical suspicion of IEM, in which a longer time is required for diagnostic workup, leading to deterioration in condition. Long term use of vitamins (cofactors) should be restricted to patients who have known metabolic errors that respond to treatment.

Table 1: Disorders that may respond to pharmacological doses of vitamins or cofactors

Cofactor	Dose	Indication
L-carnitine	100-200mg/kg/day IV	Primary carnitine deficiency, Glutaric aciduria I, Methylmalonic aciduria, Propionic aciduria, isovaleric aciduria, Carnitine acylcarnitine translocase deficiency, (Short) or Medium-chain fatty acid oxidation defects, (Mitochondrial respiratory chain disorders)
Biotin	5-10mg/day po	Biotinidase deficiency, holocarboxylase synthetase deficiency (up to 20-40mg/day), propionic aciduria
Thiamine (B1)	50 – (500) mg/day po	Maple syrup urine disease, Mitochondrial respiratory chain disorders
Riboflavin (B2)	100 – 300mg/day	Glutaric aciduria I and II, Mitochondrial respiratory chain disorders (100mg bd-tds)
Hydroxycobalamin (B12)	1mg /day IM	Methylmalonic aciduria
Coenzyme Q10	100-300mg/day	Mitochondrial respiratory chain disorders
Pyridoxine (B6)	100mg IV 50-500mg/day po	Homocystinuria, vitamin B6 responsive convulsions

Subsequent management:

Patients should not be fasted for more than 48 hours. It is necessary to continue parental administration of a high calorie diet in the form of carbohydrates and lipids (if fatty acid oxidation disorders have been ruled out), with gradual reintroduction of proteins (starting at 0.5

gram/kg/day) to prevent catabolism. Close monitoring of the acceptance of proteins is required. Administration of specific vitamins and dietary adjustments should be made once the pathology is identified.

Postmortem diagnosis

In the event of a death when a metabolic disease is suspected, it is important to take appropriate samples (Table 2) immediately before or after the death, as a conventional necropsy may not provide further clues.

Table 2: Paramortem samples (1)

Blood	Basic and special metabolic investigations should be performed if possible. If a blood sample inadequate, dried blood spots on a filter paper may be used
Urine	As much as possible, deep frozen in a plain tube
Skin	Fibroblast culture, taken with sterile precautions into a medium, stored at 4-8 degrees
Liver	Snap frozen for histochemistry or enzymology
Muscle and other tissues	As indicated, snap frozen for histochemistry or enzymology

neurological sequelae in children with inborn errors of metabolism. Better outcomes can be achieved with the use of drugs or dialysis to promote removal of toxins, and strategies to prevent catabolism. Constant vigilance and a high index of suspicion are required in identifying these children, and obtaining the appropriate biochemical parameters to allow for accurate diagnosis.

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Summary

Prompt treatment improves the survival and reduces



Radiology Quiz

Radiology Quiz

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Fig.1

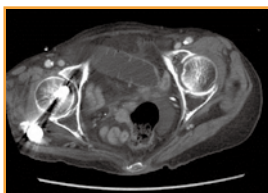


Fig.2

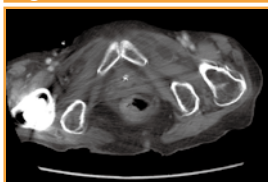


Fig.3

This patient is a 92-year-old lady with a past medical history of dementia and fractured right femur. She presented with 2 days history of repeated vomiting and colicky abdominal pain. AXR and CT abdomen were performed.

Questions:

1. What are your findings?
2. What is your diagnosis?
3. How would you manage this patient?

(See P.36 for answers)

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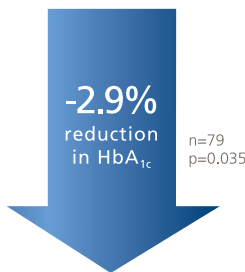
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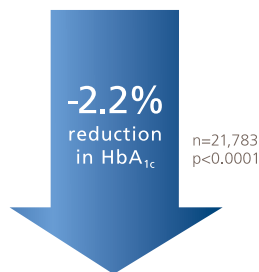
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Laboratory investigations for inborn errors of metabolism – a local perspective

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INTRODUCTION

Inborn errors of metabolism (IEM) encompass a large group of both clinically and aetiologically heterogeneous disorders involved in human biochemical metabolism. It is rather challenging to clinicians, in part there are more than 1000 different IEM such as amino acid disorders, urea cycle defects, organic acidaemias, fatty acid oxidation defects, mitochondrial disorders, carbohydrate metabolism disorders, peroxisomal disorders, purines and pyrimidines metabolism disorders, neurotransmitter disorders, transport and mineral disorders, mucopolysaccharidoses, mucopolipidoses, cholesterol and neural lipid metabolism disorders, lipid storage disorders, lysosomal disorders, and miscellaneous. Broad categories of these conditions have been attempted to classify such conditions (Table 1). More refined classifications, as in classical textbooks, could allow a breakdown based on the underlying pathophysiology. Even so, IEM can present at any age from foetus to the elderly. Their clinical presentations are protean and could be non-specific.

Table 1 Pathophysiological classification of IEM¹⁵

Group 1	Intoxication	
	Disorders <ul style="list-style-type: none"> amino acid disorders most organic acidaemias urea cycle defects (except argininase deficiency) sugar intolerance 	Typical clinical features <ul style="list-style-type: none"> normal antenatal development symptom-free period acute metabolic decompensation vomiting, lethargy, coma, liver failure intermittent attacks precipitated by metabolic stress, like infection and diarrhoea
Group 2	Energy metabolism	
	Disorders <ul style="list-style-type: none"> mitochondrial disorders encompassing respiratory chain disorders, congenital lactic acidaemias (pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, pyruvate transporter defects and Krebs cycle defects), fatty acid oxidation and ketone body defects cytoplasmic energy defects comprising glycolytic disorders, glycogen storage disorders, gluconeogenesis defects, hyperinsulinism, creatine metabolism, pentose phosphate pathway defects 	Typical clinical features <ul style="list-style-type: none"> failure to thrive hypotonia myopathy cardiomyopathy cardiac failure hepatomegaly hypoglycaemia hyperlactataemia sudden infant death
Group 3	Complex molecules	
	Disorders <ul style="list-style-type: none"> lysosomal storage disorders peroxisomal disorders congenital glycosylation disorders cholesterol synthesis defects intra-cellular trafficking disorders 	Typical clinical features <ul style="list-style-type: none"> symptoms are progressive and chronic unrelated to intercurrent events and without specific precipitating factors dysmorphism organomegaly

Table 2 Comparison of local IEM spectrum (amino acid disorders, organic acidaemias and fatty acid oxidation defects) with neighbouring populations with the commonest conditions listed below¹⁶

	Amino acid disorders	Organic acidaemias	Fatty acid oxidation defects	Overall incidence
Hong Kong¹				1 in 4,122
Incidence	69.8%	11.6%	18.6%	
Conditions	Citrin deficiency	Holocarboxylase synthetase deficiency	Carnitine-acylcarnitine translocase deficiency	
	Hyperphenylalaninaemia	Glutaric aciduria type I	Carnitine transporter defect	
	Tyrosinaemia I	Isovaleric acidaemia	Glutaric aciduria type II	
		Methylmalonic acidaemia		
Hong Kong^{2*}				1 in 5,800
Incidence	11.3%	9.7%	7.3%	
Conditions	Citrin deficiency	Holocarboxylase synthetase deficiency	Glutaric aciduria type II	
	Hyperphenylalaninaemia	Glutaric aciduria type I	Carnitine-acylcarnitine translocase deficiency	
	Ornithine carbamoyltransferase deficiency		Carnitine transporter defect	
China Mainland^{4,5}				1 in 5,800
Incidence	43.4%	50.5%	6.1%	
Conditions	Hyperphenylalaninaemia	Propionic acidaemia	Medium-chain acyl-CoA dehydrogenase deficiency	
	Ornithine transcarbamylase deficiency	Methylmalonic acidaemia	Very long-chain acyl-CoA dehydrogenase deficiency	
	Tyrosinaemia I		Glutaric aciduria type II	
Japan¹²				1 in 9,330
Incidence	21.4%	51.4%	27.2%	
Conditions	Hyperphenylalaninaemia	Propionic acidaemia	Medium-chain acyl-CoA dehydrogenase deficiency	
	Citrin deficiency	Methylmalonic acidaemia	Very long-chain acyl-CoA dehydrogenase deficiency	
		Multiple carboxylase deficiency	Glutaric aciduria type II	
Korea¹³				1 in 2,000
Incidence	42.1%	36.8%	21.1%	
Conditions	Hyperphenylalaninaemia	Propionic acidaemia	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	
	Citrullinaemia	Glutaric aciduria type I	Very long-chain acyl-CoA dehydrogenase deficiency	
	Maple syrup urine disease	Isovaleric acidaemia		
Taiwan¹⁴				1 in 5,882
Incidence	62.9%	30.0%	7.1%	
Conditions	Hyperphenylalaninaemia	3-methylcrotonyl-CoA carboxylase deficiency	Carnitine transporter defect	
	Maple syrup urine disease	Glutaric aciduria type I	Short-chain acyl-CoA dehydrogenase deficiency	
		Methylmalonic acidaemia	Medium-chain acyl-CoA dehydrogenase deficiency	

The percentages indicate the proportion of stated individual group of IEM detected in the study. * For the study by Hui et al, IEM other than amino acid disorders, organic acidaemias and fatty acid oxidation defects were included²

The truth is that IEM are collectively common contributing to a substantial patient burden albeit individually rare. No ethnic groups are spared. Our local incidence of relatively 'common' IEM was



estimated to be 1 in 4,122 to 5,800 live births in two studies.¹⁻³ The figure is similar to neighbouring and worldwide incidences such as 1 in 4,000 and 1 in 5,800 in the China Mainland.^{4,5} Relatively commoner conditions out of these studies are summarised in Table 2. This article serves to provide an overview of laboratory investigations to help in the diagnosis of these IEM, rather than going in-depth for individual disease category or condition for its diagnostication.

Initial first-line tests

These are the robust tests that could be considered in all cases with suspected IEM. They are considered first-line as being routinely available in most laboratories, and could guide subsequent investigations. They commonly include blood ammonia, lactate, glucose, arterial blood gas and acid base profile (with anion gap), ketones, electrolytes, renal and liver function tests, and complete blood picture.

For instance, significant hyperammonaemia could indicate underlying IEM conditions of urea cycle disorders and related conditions -- citrin deficiency (citrullinaemia type II), hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome and lysinuric protein intolerance, organic acidaemias, and to a lesser degree, fatty acid oxidation defects; other than liver failure due to non-IEM causes, urinary tract infection with urease-producing organisms, valproate therapy, etc. Certainly, pre-analytical factors leading to raised ammonia like difficult venepuncture, prolonged tourniquet application, sample storage at room temperature, delayed analysis and haemolysis should be considered.

Lactic acidosis is the commonest cause of high anion gap metabolic acidosis. Hyperlactataemia could signify underlying respiratory chain defects or mitochondrial disorders, citric acid (Kreb's) cycle defects, disorders of gluconeogenesis, disorders of glycogen metabolism, disorders of lactate-pyruvate metabolism (pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency); other than circulatory collapse, severe dehydration, poisoning, and tissue hypoxia due to acquired conditions.

Paired with pyruvate, the plasma lactate-to-pyruvate (L/P) molar ratio could help in delineate the causes due to disturbance in redox states of cytosols (NADH-to-NAD⁺ ratio, derived from the reversible lactate dehydrogenase reaction: lactate + NAD⁺ ↔ pyruvate + NADH + H⁺) versus pyruvate accumulation only.⁶ An elevated L/P ratio (above 25 conventionally) could signify NADH accumulation (increased NADH/NAD ratio) due to disorders of citric acid (Kreb's) cycle defects, respiratory chain defects or pyruvate dehydrogenase deficiency type B. A normal lactate-to-pyruvate ratio points to pyruvate dehydrogenase complex (PDHC) deficiency, pyruvate carboxylase deficiency type A, or gluconeogenesis defects.

Hypoglycaemia could be categorised as ketotic versus non-ketotic, and could direct concomitant tests like insulin, C-peptide, hormones like ACTH, cortisol, thyroid function test and growth hormone (in neonates/children), and/or toxicology tests if oral

hypoglycaemic drugs are suspected as the culprit. Timing for such investigations is also important, with the best time for specimen collection during acute decompensations before commencement of treatment. For the convenience of clinicians in designated sites like paediatric/neonatal intensive care units, the laboratory could prepare and adopt investigation kits for suspected IEM, with instructions for sample collections to ensure the specimens are properly collected, transported and stored, for subsequent investigations of IEM if necessary. An example of the contents of our metabolic investigation kit is shown in Figure 1.

Figure 1: Contents of Metabolic Investigation Kit

1a: Specimen containers in a kangaroo bag

- Pyruvate collection kit
 - Pre-weighed perchloric acid bottle x 1
 - 1mL syringe x 1
 - Plain bottle x 1
 - Instruction sheet
- 4mL red-cap plain bottle x 1
- Small Li-heparin bottle x 2
- Small fluoride bottle x 1
- Small EDTA bottle x 2
- 10mL plain tube for spot urine x 1

1b: Plastic clipped container of the metabolic kit with instruction sheet



1c: laboratory form

Patient/Guard Label		Metabolic Emergency Investigation Kit ()
Name: _____		Perchloric acid = 1
Date: _____		Clotted blood = 1
Referring Doctor Name: _____		Li-Heparin = 2
Special Instructions: _____		Fluoride = 1
_____		EDTA = 2
_____		Urine (3-tubes) = 1

Notes for the accompanying request on container

- Samples for ammonia investigations should be collected before any treatment is given.
- Samples collected using this kit will be stored properly for subsequent analysis if necessary. This form will be returned. Please send separate samples for laboratory investigation as appropriate.
- For test arrangements, please contact Dr. Yee (phone at 2461 2471). All other office hours, enquiries will be directed to the clinical laboratory services.

The earlier practices for metabolic screening tests, usually based on chemical reactions and subsequent colour changes, like Berry's test, clinitest, ninhydrin test, ferric chloride test, nitroprusside-cyanide test, nitrosonaphthanol test, etc., were largely limited by their non-specificities, prone to multiple interferences by both endogenous and exogenous compounds, and subjective interpretation. Therefore, they have largely been superseded and should be of limited use as part of the IEM screening investigation protocol.

Further investigations

Further tests could be considered when the first-line tests hinted to the possibility of IEM. These commonly include plasma amino acids, urine amino acids, urine organic acids and plasma acylcarnitines. These are

particularly helpful in the biochemical diagnosis of amino acid disorders, organic acidurias and fatty acid oxidation defects. For amino acid profiling, usually only a plasma sample would suffice, except conditions where renal amino acid transport anomaly is suspected in cases like the Fanconi's syndrome or cystinuria, in which paired urine samples are necessary.

Urine for reducing sugars, using chromatography-based methodology, could delineate IEM such as galactosaemia and hereditary fructose intolerance. Oligosaccharides represent glycosidic groups of glycoproteins and glycogen degraded by the lysosomal enzymes. Deficiencies in these enzymes lead to the group of lysosomal storage diseases collectively known as the oligosaccharidoses. Detection of abnormal pattern of oligosaccharides could aid in identification of lysosomal storage diseases like α -mannosidosis, GM1 gangliosidosis, infantile sialidosis, aspartylglucosaminuria, mucopolysaccharidosis type I, and certain types of mucopolysaccharidosis and glycogen storage diseases.

For suspicion of particular diseases, specific biochemical tests should be ordered and here are some examples. In cases of congenital disorder of glycosylation, transferrin isoforms should be tested in blood. For biotinidase deficiency, the activity of biotinidase could be measured in serum. For sitosterolaemia, plant sterol analysis in blood should be ordered. For cerebrotendinous xanthomatosis, blood for cholestanol should be tested. For peroxisomal disorders like the Zellweger syndrome and X-linked adrenoleukodystrophy, plasma very long chain fatty acids, pristanic acid and phytanic acids should be considered. A urine sulphite test could be ordered for suspected cases of molybdenum cofactor deficiency or sulfite oxidase deficiency, a supplementary metabolic screen for sick children presented with unexplained therapy-resistant seizures. Table 3 summarises the primary IEM indications for these second-tier tests available within chemical pathology laboratories in local public hospitals.

Using gas chromatography-mass spectrometry (GC-MS), organic acid profile could be studied in biological fluids especially urine. This test is complex, both technically and interpretatively. Technically, hundreds of compounds are excreted in normal subjects, while informative markers could only be found in a few out of the many, further dependent on the clinical status. The coverage of such varieties of compounds with different solubilities and volatilities is challenging. In some laboratories, a unified and expanded GC-MS protocol for major diagnostic metabolites in urine, including amino acids, organic acids, monosaccharides, di-saccharides, purines, and pyrimidines, has been in-house formulated.⁷ The broad-spectrum GC-MS profiling method shows the unique advantage of detecting abnormal metabolites of different chemical classes related to each IEM in a single run, e.g. abnormal amino acids plus orotic acids in urea cycle defects; abnormal galactose, galactitol, galactonate plus secondary amino acid changes in galactosaemia. It also adds values to the screening of highly polar diagnostic compounds, e.g. glycolic acid and glyceric acid for primary hyperoxalurias.

Table 3 A brief survey of second-tier (non-genetic) tests for IEM currently provided by clinical biochemistry/chemical pathology laboratories in public hospitals in Hong Kong

Test name	Disorders	Sample types	List of HA providers
Amino acids	<ul style="list-style-type: none"> Disorders of amino acid metabolism and transport Cystinuria (for urine) 	Blood, urine, DBS, CSF	QMH, QEH, PMH, PWH
Organic acids	<ul style="list-style-type: none"> Organic acidurias Orotic aciduria Primary lactic acidurias Fatty acid oxidation defects Disorders of ketogenesis and ketolysis Primary hyperoxalurias 	Urine	QMH, PMH, PWH, TMH
Acylcarnitines	<ul style="list-style-type: none"> Fatty acid oxidation defects 	Blood, DBS	QMH, PMH, PWH
Purine, pyrimidines	<ul style="list-style-type: none"> Disorders of purine and pyrimidine metabolism 	Urine	PMH, QMH
Reducing substances	<ul style="list-style-type: none"> Galactosaemia Disorders of fructose metabolism 	Urine	QMH, PMH, PWH, PYNEH, QEH
Oligosaccharides	<ul style="list-style-type: none"> Oligosaccharidoses 	Urine	PMH
Very long chain fatty acids, +/- phytanic and pristanic acids	<ul style="list-style-type: none"> Peroxisomal disorders like Zellweger syndrome, Rhizomelic chondrodysplasia punctata, Refsum's disease, X-linked adrenoleukodystrophy, etc. 	Blood	QMH, PWH
Biotinidase activity	<ul style="list-style-type: none"> Biotinidase deficiency 	Blood	QMH, PWH
Glycosaminoglycans	<ul style="list-style-type: none"> Mucopolysaccharidosis 	Urine	QMH, PWH, PMH, QEH
Mucopolysaccharide pattern	<ul style="list-style-type: none"> Mucopolysaccharidosis 	Urine	PMH, QMH
Chitotriosidase	<ul style="list-style-type: none"> Gaucher disease Sphingolipidoses like Niemann-Pick disease, Krabbe disease, GM1-gangliosidosis 	Blood	QMH
Transferrin isoforms	<ul style="list-style-type: none"> Congenital disorder of glycosylation 	Blood	PWH
Plant sterols	<ul style="list-style-type: none"> Sitosterolaemia 	Blood	QMH
Neurotransmitters	<ul style="list-style-type: none"> Disorders of tyrosine hydroxylase deficiency, aromatic L-amino acid decarboxylase (AADC) deficiency and cerebral folate deficiency 	CSF	QMH
Pterins	<ul style="list-style-type: none"> Disorders of tetrahydrobiopterin (BH4) especially those with hyperphenylalaninaemia 	Urine, CSF	QMH, PMH*
Porphobilinogen (PBG), porphyrin	<ul style="list-style-type: none"> Acute porphyria screening for PBG Porphyria screening for urine porphyrins 	Urine	QMH, QEH, PMH, PWH, PYNEH, TMH
Porphyria fractionation	<ul style="list-style-type: none"> Identification of types of porphyria 	Blood, urine, faeces	QMH, PMH
Apolipoproteins, lipoprotein pattern	<ul style="list-style-type: none"> Disorders of lipid metabolism 	Blood	QMH
Total bile acids	<ul style="list-style-type: none"> Disorders of bile acid metabolism 	Blood	QMH

PYNEH: Pamela Youde Nethersole Eastern Hospital, PMH: Princess Margaret Hospital, PWH: Prince of Wales Hospital, QEH: Queen Elizabeth Hospital, QMH: Queen Mary Hospital, TMH: Tuen Mun Hospital.

* Urine only, qualitative

Cerebrospinal fluid (CSF) analytes and neurotransmitters

While lumbar puncture is an invasive procedure requiring an informed consent, it could play a role in particular for a few IEM conditions. Isolated from blood by the blood-brain barrier, the distribution of biochemical components like glucose would create a physiological gradient. Therefore, paired blood and CSF specimens would be required. CSF could allow analysis of multiple parameters, notably glucose, lactate, amino acids and neurotransmitter profile, for diagnosis of a few IEM conditions. For instance, hypoglycorrhachia (low CSF glucose concentration)



with a low CSF-to-blood glucose ratio (<0.5), in the absence of hypoglycaemia and infection of the central nervous system, could signify glucose transport defects due to the glucose transport deficiency syndrome (GLUT1 deficiency). Lactate in CSF is more sensitive than plasma lactate in mitochondrial respiratory chain disorders and can be checked if plasma lactate is normal and the clinical suspicion is high; amino acid profile in CSF could be helpful in nonketotic hyperglycaemia, serine deficiency, pyridoxamine-5-phosphate oxidase deficiency (raised glycine and threonine), neurotransmitter profile in CSF could help in diagnosis of disorders of tyrosine hydroxylase deficiency, aromatic L-amino acid decarboxylase (AADC) deficiency and cerebral folate deficiency. Both CSF and urine pterin analysis can detect biopterin metabolism with hyperphenylalaninaemia, like GTP cyclohydrolase (GTPCH) deficiency, 6-pyruvoyl-tetrahydropterin tetrahydropterin synthase (PTPS) deficiency, and pterin-4 α -carbinolamine dehydratase (PCD) deficiency. In our experience, low urine homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) by GC-MS could be identified in patients with tyrosine hydroxylase deficiency and AADC deficiency.⁸⁻¹⁰

Enzyme study

Theoretically, checking for enzyme activity causing particular IEM disease entity could be considered, if available. However, there are only a few conditions which enzymes could be measured using peripheral blood or skin fibroblast with commercially available test kits. Examples with more established role in biochemical diagnosis include lysosomal storage diseases --- α -galactosidase A activity for Fabry's disease, α -glucosidase activity in Pompe, hexosaminidases for Tay-Sachs and Sandhoff disease, galactosylceramidase activity in Krabbe disease, arylsulfatase A in metachromatic leukodystrophy, enzyme complexes (complex I, II, III, IV, V), pyruvate dehydrogenase for mitochondrial disorders, etc. However, most of these tests are not available in local laboratories. Specialised or tertiary laboratories would be required to provide and sustain the service.

Dried blood spot for symptomatic screening

Dried blood spot(DBS) is widely adopted as universal screening programme for all newborns in many parts of the world. The technology allows relatively inexpensive simultaneous detection of more than 30 different metabolic disorders in one single blood spot specimen with satisfactory analytical accuracy and precision.¹¹ The ease of collection (whole blood collected at commercial Whatman 903 filter paper upon heel pricking) and requirement of much less blood volume could be advantageous for the paediatric age group. Its clinical use could be further extended as a broad spectrum metabolic screening, which has been extensively studied internationally for its commendable diagnostic performance, for various disorders in amino acids, urea cycle, fatty acid oxidation and organic acids metabolism, in one goal.

Genetic analysis

If a particular disease could be suggested by the prior investigations, and there is/are particular gene(s) known to be causative, genetic analysis of such gene(s) could be pursued, in an attempt to confirm the diagnosis genetically. The increasing availability of such tests, from the Clinical Genetic Service, Department of Health, universities, regional hospitals to private laboratories, could facilitate so. The challenge would be conditions with multiple causative genes or large genes, gene-gene interactions, presence of unknown genes, non-causative disease-modifying genes, incomplete penetrance, genetic variants of uncertain significance, ethical/social considerations and resources required, to have confined the scope of genetic tests. On the other hand, the facilitation of prenatal diagnosis, family screening of at-risk members and technological advances have pushed genetic confirmation further. Advances of techniques like array comparative genomic hybridisation (CGH), next generation sequencing, could even extend the boundary of this further.

Acknowledgement: We would like to thank our sister HA laboratories contributing to the list of laboratory tests concerning inborn errors of metabolism as depicted in Table 3.

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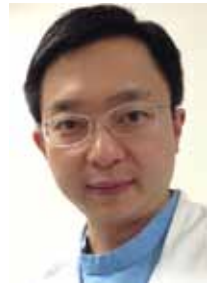
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Paediatric Neurotransmitter Diseases (PNDs) Due to Disorders in the Biogenic Amine Pathway



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Paediatric Neurotransmitter Diseases (PNDs) are a heterogeneous group of rare inherited neurometabolic disorders in which the synthesis, breakdown or transport of neurotransmitters are affected.¹

Biogenic amines are important neurotransmitters in the central and peripheral nervous system. Dopamine plays key roles in the control of voluntary movements, cognition and behaviour while serotonin is important in controlling sleep, body temperature, appetite, memory and many endocrine functions.^{2,3} PNDs comprise of a wide spectrum of clinical features that may mimic other neurological conditions such as cerebral palsy, hypoxic-ischaemic encephalopathy, movement disorders, neuromuscular diseases, seizures, mitochondrial cytopathies and other inherited metabolic disorders.

In view of wide phenotypic manifestations, the diagnosis of PNDs may be difficult. However, recognition of PNDs is still crucial as good clinical responses can be achieved in many PNDs.

Biogenic Amine Pathway

The biogenic amine biosynthesis involves hydroxylation of tyrosine and tryptophan to L-dopa and 5-hydroxytryptophan (5-HTP) followed by decarboxylation to form dopamine and serotonin, respectively. Dopamine can be further converted to norepinephrine and epinephrine. [Figure 1.]

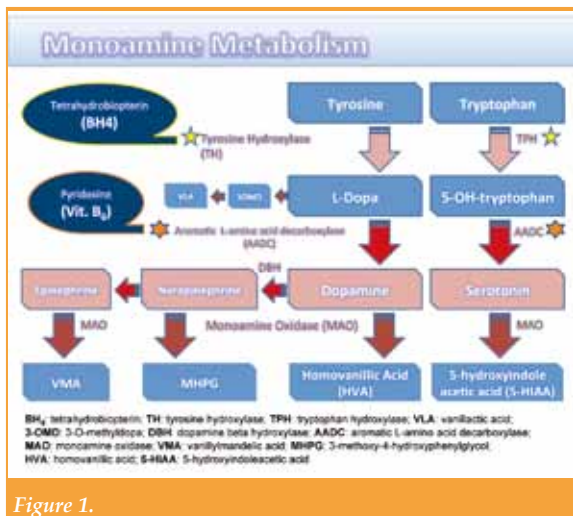


Figure 1.

Tetrahydrobiopterin (BH₄) is the co-factor for tyrosine and tryptophan hydroxylation. Defects in synthesis or regeneration of BH₄ will therefore affect biogenic amine biosynthesis. BH₄ also affects hydroxylation of phenylalanine and this explains why hyperphenylalaninaemia (HPA) is present in some BH₄ metabolism disorders. [Figure 2.]

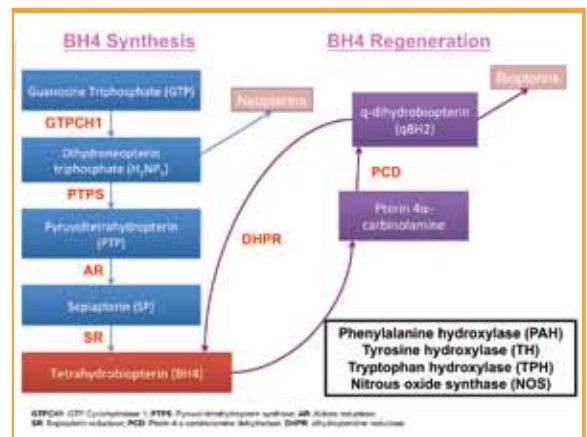


Figure 2.

Clinical Manifestations of PNDs^{2,4,5,6}

Symptoms of dopamine deficiency include oculogyric crisis, truncal hypotonia, limbs spasticity, dystonia, parkinsonism, tremor and chorea. Epileptic encephalopathy, progressive cognitive dysfunction, feeding difficulties and microcephaly are also noted in PNDs with dopamine deficiency. Catecholamine deficiency may result in ptosis, miosis, sweating, excessive salivation and nasal/oropharyngeal secretions, bradyarrhythmia and hypotension. Clinical manifestations of serotonin deficiency are less well defined and may include sleep disturbances, unstable body temperature and possibly dystonia.

Specific Disorders of Biogenic Amine Pathway

BH₄ Deficiency without HPA

Autosomal Dominant Guanosine Triphosphate Cyclohydrolase 1 (GTPCH1) Deficiency
 Autosomal dominant GTPCH1 deficiency, also known as Segawa Disease⁷, is the most widely described PND.

GTPCH1 is the rate-limiting enzyme in BH₄ synthesis. Classical phenotype is characterised by childhood-onset exercise-induced dystonia typically affecting the lower limbs and later with tremor, diurnal variation with worsening of symptoms towards the end of the day and the absence of cognitive impairment.^{4,5} Biochemically, it is characterised by low HVA, normal or low 5-HIAA and reduced neopterin and biopterin in CSF and normal serum phenylalanine level. Treatment response to combined levodopa/carbidopa is usually excellent.

Sepiapterin Reductase (SR) Deficiency

SR is involved in the final step of BH₄ biosynthesis. HPA is not present as other enzymes can also convert 6-pyruvoyltetrahydropterin to BH₄ in peripheral tissues.^{8,9} Clinical features include parkinsonism, dystonia, hypotonia, spasticity, ataxia, choreoathetosis, oculogyric crises, psychomotor retardation, unstable body temperature, hypersalivation, irritability, aggression and depression. Many symptoms show diurnal variations. Biochemically, HVA and 5-HIAA are reduced while biopterin and sepiapterin are raised in CSF. Urine pterins are generally normal. Treatment with L-dopa and 5-HTP usually result in good response.^{5,6}

BH₄ Deficiency with HPA

Autosomal Recessive GTPCH1 Deficiency

This accounts for a minority of all cases of GTPCH1 deficiencies. Patients usually present in infancy with severe developmental delay, truncal hypotonia, limbs hypertonia, dystonia, seizures and autonomic dysfunctions.^{5,6} CSF HVA and 5-HIAA are low. Neopterin and biopterin in CSF are reduced. In contrast to the autosomal dominant form, serum phenylalanine level is raised. Treatment with BH₄ is required. Since BH₄ entering the brain cannot sustain adequate production of neurotransmitters, L-dopa and 5-HTP are usually given.⁶

6-Pyruvoyl Tetrahydropterin Synthase (PTPS) Deficiency

PTPS deficiency is the most common disorder in BH₄ deficiency.⁶ The estimated prevalence of HPA due to PTPS deficiency in Hong Kong was reported to be 1 in 29,542 live births whereas no single case of classical phenylketonuria has been reported.^{10,11}

Patients with PTPS deficiency are classified into typical/severe form (HPA and abnormal CSF neurotransmitters; ~80%) or atypical/peripheral form (minor/no changes in CSF neurotransmitters and mild/transient HPA; ~20%).^{6,12} In countries with newborn screening for PKU, PTPS deficiency could be picked up by neonatal dried blood spot analysis.

Patients have HPA and raised neopterin, reduced biopterin, low HVA and 5-HIAA in CSF. Urine for pterins shows increases in neopterin and neopterin-to-biopterin ratio and reduction of biopterin.^{5,6}

Patients usually present in early infancy with severe psychomotor retardation, central hypotonia, spastic extremities, lack of eye contact, bradykinesia and seizures. They may also have failure to thrive, microcephaly, mousy odour, fair complexion and blond hair.^{6,12}

Clinical outcomes are excellent for the mild form after BH₄ treatment. In severe disease, early treatment with BH₄, L-dopa and 5-HTP were reported to be associated with satisfactory outcomes. Even in those with delayed treatment, improvements in neurological status and intelligent/developmental quotient were observed in all patients.^{5,6,12}

Dihydropteridine Reductase (DHPR) Deficiency

It is thought to be the more severe form of pterin metabolism disorder.¹³ Clinical presentation is similar to PTPS deficiency with onset in the neonatal period or early infancy.⁶ DHPR is important in maintaining folate in its active form and depletion in central nervous system folate may contribute to the more severe phenotype.⁶ All patients have HPA and low CSF HVA, 5-HIAA, 5-methyltetrahydrofolate (5-MTHF) and raised CSF biopterin.

Good clinical outcomes can usually be achieved with early BH₄, L-dopa and 5-HTP treatment. Other agents such as monoamine oxidase inhibitor (MAOI) may be used. In severely affected patients, a phenylalanine-restricted diet is given to normalise phenylalanine level. Folinic acid supplement is generally recommended to counteract folate depletion.^{5,6}

Disorder of Biogenic Amine Synthesis

Tyrosine Hydroxylase (TH) Deficiency

In 2010, our group reported 12 Chinese patients with TH deficiency in Hong Kong.¹⁴ In fact, more cases were identified in the last few years.

Patients may present with hypokinesia, rigidity, dystonia, chorea, tremor, ptosis, oculogyric crises and hypersalivation. Clinical phenotypes are classified into type A (infantile hypokinetic rigid syndrome and dystonia with onset in infancy or childhood; ~70%) and type B (severe complex encephalopathy with onset in neonatal period or early infancy; ~30%) subtypes.^{6,15}

Neurotransmitters analysis shows low HVA, reduced HVA to 5-HIAA ratio and normal 5-HIAA in CSF.^{14,15,16} Hyperprolactinaemia is found in 50% of cases with severe phenotype.¹⁴

L-dopa is the mainstay of treatment and early addition of selegiline results in remarkable responses in some patients. Beneficial responses can usually be observed in Type A patients within the first 2 weeks of treatment whereas the positive effect often occurs later in Type B patients.¹⁵ Even if there is a treatment delay of years after onset of neurological symptoms, treatment response is still good in patients with mild phenotype.¹⁴

Aromatic L-amino acid Decarboxylase (AADC) Deficiency

Deficiency of AADC will lead to reduced catecholamines and serotonin. Symptoms usually begin in early infancy. Generalised hypotonia and oculogyric crises are the most consistent neurological symptoms. Approximately 50% of cases have movement disorders, namely dystonia, choreoathetosis, rigidity and bradykinesia. Patients frequently have feeding difficulties. Diaphoresis and nasal congestion are common autonomic dysfunctions. Many patients also have irritability, failure to thrive



Disorders	Inheritance	Serum Phenylalanine	CSF HVA	CSF 5-HIAA	CSF 3-OMD	CSF 5-MTHF	CSF Septapterin	CSF Neopterin	CSF Biopterin
BH4 Synthesis									
GTPCH1 Deficiency	AD	N	↓	±↓	N	N	N	↓	↓
GTPCH1 Deficiency	AR	↓	↓	N	N	N	N	↓	↓
PTPS Deficiency	AR	↓	↓	↓	N	N	N	↓	↓
SR Deficiency	AR	N	↓	↓	N	N	↑	↑	↑
BH4 Regeneration									
PCD Deficiency	AR	↓	N	N	N	N	N	N	N
DHPR Deficiency	AR	↓	↓	↓	N	↓	N	N	↓
Monoamine synthesis									
TH Deficiency	AR	N	↓	N	N	N	N	N	N
TPH Deficiency	AR	N	N	↓	N	N	N	N	N
AADC Deficiency	AR	N	↓	↓	↓	N	N	N	N
Monoamine Transport									
DTDS	AR	N	↑	N	N	N	N	N	N

BH4: tetrahydrobiopterin; GTPCH1: GTP cyclohydrolase I; PTPS: 6-pyruvoyltetrahydropterin synthase; SR: sepiapterin reductase; PCD: pterin 4 α -carbinolamine dehydratase; DHPR: dihydropteridine reductase; TH: tyrosine hydroxylase; TPH: tryptophan hydroxylase; AADC: aromatic amino acid decarboxylase; DTDS: dopamine transporter deficiency syndrome; AD: autosomal dominant; AR: autosomal recessive

Table 1.

and sleep disturbances and the majority have profound cognitive impairments.^{6,17}

Low CSF HVA and 5-HIAA and elevated 3-O-methyldopa (3-OMD) are characteristic findings. Urine organic acid analysis to detect low vanillylmandelic acid (VMA) or high vanillic acid (VLA) and the presence of 3-OMD has been advocated as a screening tool.^{6,18} Since AADC is a pyridoxine-dependent enzyme, inherited vitamin B₆ metabolism disorder may show similar CSF findings as AADC deficiency though its clinical phenotype is mainly intractable neonatal epileptic encephalopathy.

Treatment with co-factor supplements (e.g. pyridoxine), dopamine agonists (e.g. bromocriptine or pergolide) and MAOI (e.g. selegiline) are frequently tried. However, treatment response is generally poor and similar outcomes were also observed in local cases.⁵

Disorder of Biogenic Amine Transport

Dopamine Transporter Deficiency Syndrome (DTDS)

Patients with DTDS due to *SLC6A3* mutation can present with either hyperkinesia or parkinsonism, or even a mixed hyper-/hypo-kinetic movement disorder in early infancy. During childhood, patients develop severe parkinsonism-dystonia associated with abnormal eye movements and pyramidal tract features. Contrary to other dopamine biosynthesis disorders, DTDS is characterised by increases in CSF HVA and elevated HVA to 5-HIAA ratio. Hyperprolactinaemia and high serum creatine kinase are also seen in some cases. Treatment response is generally poor in DTDS.⁶

Diagnosis of PNDs

Early clinical suspicion and appropriate investigations are essential for accurate diagnosis.⁶ Diagnosis of biogenic amine metabolism disorders usually requires analysis of CSF neurotransmitter metabolites. [Table 1]

Attention must be paid on interpretation of CSF neurotransmitter analysis as secondary causes for monoamine neurotransmitter depletion have been reported in other neurological disorders such as hypoxic-ischaemic encephalopathy, epilepsy, mitochondrial

diseases, leukodystrophies, Rett's syndrome, phenylketonuria, pontocerebellar hypoplasia, etc.⁶

Plasma and urine pterins, urine organic acids, plasma amino acids (e.g. phenylalanine) are useful as screening tests or aid in diagnosis of PNDs. Confirmation of diagnosis could be made by measurement of the enzyme activity whenever possible and/or more often by mutational analysis in this locality.

Dopamine inhibits prolactin release. Serum prolactin level therefore could be raised in dopamine deficiency states in some PNDs. Prolactin could act as a marker of the disease and may aid in monitoring of treatment if the baseline prolactin is elevated.

CSF Collection for Neurotransmitter Metabolites

CSF collection for diagnosing PNDs should follow a specific procedure and requires careful handling and processing. Traumatic spinal tap has to be avoided as breakage of red cells in CSF will lead to rapid oxidation of neurotransmitter metabolites. CSF contaminated with blood must be therefore centrifuged immediately before further processing.³ There is a rostrocaudal gradient of neurotransmitter metabolites and pterins in CSF. The more CSF is drawn, the higher will be the levels of neurotransmitter metabolites with values almost doubled with every 5 to 10 ml CSF drawn.^{3,4} Therefore, a same fraction of CSF should be used for analysis and findings should be compared with the age-matched references developed by using the same collection protocol. CSF collected should be frozen and protected from light immediately and mixed with antioxidant to prevent pterin degradation before analysis.¹

Conclusion

PNDs are a group of rare inherited neurometabolic diseases that usually present in infancy or early childhood. Motor dysfunction and parkinsonism are the most characteristic manifestations of PNDs.¹

Some non-invasive laboratory tests such as urine organic acid analysis, plasma phenylalanine and prolactin levels are useful screening tests. Further confirmation requires specific CSF analysis for neurotransmitter metabolites and mutational analysis. Expanded newborn screening with dried blood spot analysis could also help in early identification of some potentially treatable PNDs (e.g. PTPS deficiency).

Many PNDs are amendable to treatment. Early treatment can bring about positive changes in patients' lives while delayed treatment is more often associated with poor motor and cognitive outcomes. Screening of PNDs should therefore be seriously considered and performed early in patients with motor dysfunction (e.g. severe hypotonia), progressive encephalopathy, developmental delay or regression, movement disorders such as parkinsonism, with or without seizures, particularly when these signs and symptoms cannot be explained by other aetiologies.

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7 Jan	Mediation and healthcare	Dr. TSOI Chun Hing Ludwig 蔡振興 Senior Medical Officer 高級醫生 Accredited Mediator 認可調解員
14 Jan	Negotiation skills and empowerment	Mr. LAI Tsz Kin Jacky 黎子健 Barrister-at-law 大律師 Accredited Mediator 認可調解員
21 Jan	Listening skills and use of body language	Prof. LAI Bo San Paul 賴寶山 Professor 教授 Accredited Mediator 認可調解員
28 Jan	Perception check, paraphrasing and summarizing skills	Dr. DAI Lok Kwan David 戴樂群 Consultant 顧問醫生 Accredited Mediator 認可調解員
4 Feb	Reframing and facilitative skills	Dr. ONG Kim Lian 王金蓮 Consultant 顧問醫生 Accredited Mediator 認可調解員
11 Feb	Deadlock and impasse	Dr. CHAN Lap Wa 陳立華 Consultant 顧問醫生 Accredited Mediator 認可調解員

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4	5	6
<ul style="list-style-type: none"> Lantau Hiking Team (Shek Pik to Tai O) Season's Greetings to Hong Chi (香林送暖到匡智) 	<ul style="list-style-type: none"> FMSHK Officers' Meeting HKMA Council Meeting 	<ul style="list-style-type: none"> HKMA Shatin Doctors Network - Reference Framework for Preventive Care for Older Adults in Primary Care Settings 	<ul style="list-style-type: none"> HKMA Hong Kong East Community Network - HPV Vaccination - The Urologists Perspective HKMA New Territories West Community Network - Latest Update on COPD Management The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses 	<ul style="list-style-type: none"> 21st Annual Scientific Meeting - Degenerative Lumbar Spine HKMA Shatin Doctors Network - Recommendation on Herpes Zoster Vaccination for Adults HKMA Gourmet Dinner 	<ul style="list-style-type: none"> 21st Annual Scientific Meeting - Degenerative Lumbar Spine HKMA Yau Tsim Mong Community Network - Current Management of Gouty Arthritis 	<ul style="list-style-type: none"> 21st Annual Scientific Meeting - Degenerative Lumbar Spine HKDMA Symposium 2014 - Our Preparedness and Response in Marine Disasters
	8	9	10	11	12	13
	<ul style="list-style-type: none"> HKMA Yau Tsim Mong Community Network - New Understanding on Osteoporosis Management - Significance of Tailored Treatment for Better Patient Compliance 	<ul style="list-style-type: none"> Hong Kong Neurosurgical Society Monthly Academic Meeting - Management of Drug Resistant Epilepsy HKMA Shatin Doctors Network - Helping the Man with Premature Ejaculation: Our Responsibility 	<ul style="list-style-type: none"> HKMA Hong Kong East Community Network - Recent Advances in the Management of Peripheral Vascular Disease & Varicose Veins The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses HKMA Structured CME Programme with Hong Kong Government & Hospital Management of Lung Shadow 	<ul style="list-style-type: none"> HKMA Hong Kong East Community Network - Recent Advances in the Management of Peripheral Vascular Disease & Varicose Veins The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses HKMA Structured CME Programme with Hong Kong Government & Hospital Management of Lung Shadow 	<ul style="list-style-type: none"> HKMA Yau Tsim Mong Community Network - Current Management of Gouty Arthritis 	<ul style="list-style-type: none"> Refresher Course for Health Care Providers 2014/2015 - Workshop on Stress management through the lifespan
	15	16	17	18	19	20
		<ul style="list-style-type: none"> HKMA Kowloon West Community Network - A New Paradigm in the Management of Acute Coronary Syndrome 	<ul style="list-style-type: none"> HKMA Central, Western & Southern Community Network - Diagnosis and Management of Carpal Tunnel Syndrome 	<ul style="list-style-type: none"> The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses FMSHK Executive Committee Meeting 	<ul style="list-style-type: none"> KECN/UCH - Certificate Course for GPs 2014 - Parkinsonism and Other Movement Disorders 	
	22	23	24	25	26	27
			<ul style="list-style-type: none"> FMSHK Annual Dinner 2014 HKMA Annual Ball 2014 			
	29	30	31			
	7	14	21	28		



Date / Time	Function	Enquiry / Remarks
2 TUE	8:00 pm FMSHK Officers' Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F., Hong Kong Jockey Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
	8:00 pm HKMA Council Meeting Organiser: The Hong Kong Medical Association; Chairman: Dr. SHIH Tai Cho, Louis; Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
3 WED	1:00 pm HKMA Shatin Doctors Network - Reference Framework for Preventive Care for Older Adults in Primary Care Settings Organisers: HKMA Shatin Doctors Network & Primary Care Office of the Department of Health; Chairman: Dr. MAK Wing Kin; Speaker: Prof. WONG Chi Sang, Martin; Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG Tel: 2527 8285 1 CME Point
4 THU	1:00 pm HKMA Hong Kong East Community Network - HPV Vaccination - The Urologist's Perspective Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. KONG Wing Ming, Henry; Speaker: Dr. YIP Wai Chun, Andrew; Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
	1:00 pm HKMA New Territories West Community Network - Latest Update on COPD Management Organiser: HKMA New Territories West Community Network; Chairman: Dr. LEE Huen; Speaker: Dr. LEE Chi Hang, Clarence; Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家), 1/F., Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
	1:30 pm The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses Organisers: Hong Kong Medical Association & Department of Health; Speaker: Prof. Stanley S. C. HUI / Mr. Sam W. S. WONG; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2 CME Points
5 FRI	9:00 am - 5:00 pm (6) 21st Annual Scientific Meeting - Degenerative Lumbar Spine Organiser: Hong Kong Neurosurgical Society; Speakers: Prof. Kang LU, Prof. Dong Ah SHIN, Prof. Keith D LUK & Dr. David SUN; Venue: Langham Hotel, 8 Peking Road, TST, Kowloon	Ms. Shirley MA Tel: 2468 5402
	1:00 pm HKMA Shatin Doctors Network - Recommendation on Herpes Zoster Vaccination for Adults Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. WU Yee Ming; Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Sandy CHUNG Tel: 3971 2930 CME Point t.b.c.
	7:30 pm HKMA Gourmet Dinner Organiser: The Hong Kong Medical Association; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Building, 21-22 Connaught Road, Central	Mr. Benjamin CHAN Tel: 2527 8285
6 SAT	1:30pm HKDMA Symposium 2014 - Our Preparedness and Response in Marine Disasters Organiser: The Hong Kong Disaster Medicine Association Ltd; Chairman: Dr. LUK Wei Kwang; Venue: Lecture Theatre, M/F, Hospital Authority Building, 147B Argyle Street, Kowloon	Enquiry: info@hkdma.org
7 SUN	10:00 am Lantau Hiking Team (Shek Pik to Tai O) Organiser: The Hong Kong Medical Association; Chairman: Dr. SIN Pui Yee, Helena; Venue: Lantau Island	Mr. Benjamin CHAN Tel: 2527 8285
	1:30 pm Season's Greetings to Hong Chi (杏林送暖到匡智) Organiser: The Hong Kong Medical Association; Chairman: Dr. SHIH Tai Cho Louis; Venue: Hong Chi Pinehill Village(匡智會松嶺村), Pinehill Village, Chung Nga Road, Nam Hang, Tai Po	Miss Hana YEUNG Tel: 2527 8285
9 TUE	1:00 pm HKMA Yau Tsim Mong Community Network - New Understanding on Osteoporosis Management - Significance of Tailored Treatment for Better Patient Compliance Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHAN Wai Keung; Speaker: Dr. TSANG Man Wo; Venue: Nathan Room 3-Hall, Level 1, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
10 WED	7:30 am Hong Kong Neurosurgical Society Monthly Academic Meeting - Management of Drug Resistant Epilepsy Organiser: Hong Kong Neurosurgical Society; Chairman: Dr. ZHU Xian Lun; Speaker: Dr. CHAN Yuen Chung, David; Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 1.5 Points
	1:00 pm HKMA Shatin Doctors Network - Helping the Man with Premature Ejaculation: Our Responsibility Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. FUNG Tat Chow, Berry; Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Karen WONG Tel: 3605 5843 CME Point t.b.c.
11 THU	1:00 pm HKMA Hong Kong East Community Network - Recent Advance on the Management of Peripheral Arterial Disease & Varicose Veins Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. LAM See Yui, Joseph; Speaker: Dr. TSE Cheuk Wa, Chad; Venue: HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 CME Point t.b.c.
	1:30 pm The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses Organisers: Hong Kong Medical Association & Department of Health; Speaker: Mr. Sam W. S. WONG; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2 CME Points
	2:00 pm HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2014 - Management of Lung Shadow Organisers: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. LAM Bing; Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
12 FRI	1:00 pm HKMA Yau Tsim Mong Community Network - Current Management of Gouty Arthritis Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHAN Wai Kwong; Speaker: Dr. TSUI Hing Sum; Venue: Jade Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point



Date / Time	Function	Enquiry / Remarks
13 SAT 2:15 pm	Refresher Course for Health Care Providers 2014/2015 - Workshop on Stress management through the lifespan Organisers: Hong Kong Medical Association & HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital; Speaker: Dr. LAM Wing Wo; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
16 TUE 1:00 pm	HKMA Kowloon West Community Network - A New Paradigm in the Management of Acute Coronary Syndrome Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LEUNG Gin Pang; Speaker: Dr. WONG Wing Kwong, Raymond; Venue: Crystal Room I-III, 30/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
17 WED 1:00 pm	HKMA Central, Western & Southern Community Network - Diagnosis and Management of Carpal Tunnel Syndrome Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. POON Man Kay; Speaker: Dr. LAU Shun Chung, Jacky; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
18 THU 1:30 pm	The Hong Kong Medical Association Community Network Exercise Prescription Certificate Courses Organisers: Hong Kong Medical Association & Department of Health; Speaker: Ms. Joey CHENG; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2 CME Points
	8:00 pm FMSHK Executive Committee Meeting Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
19 FRI 1:00 pm	KECN/UCH – Certificate Course for GPs 2014 - Parkinsonism and Other Movement Disorders Organisers: HKMA Kowloon East Community Network & United Christian Hospital; Chairman: Dr. LEUNG Man Fuk; Speaker: Dr. CHEUNG Ka Yin; Venue: East Ocean Seafood Restaurant, Shop 137, 1/F, Metro City Plaza 3, 8 Mau Yip Road, Tseung Kwan O, KLN	Ms. Polly TAI Tel: 3513 3430 Ms. Cordy WONG Tel: 3513 3087 Fax: 3513 5505 1 CME Point
31 WED 7:00 pm	FMSHK Annual Dinner 2014 Organiser : The Federation of Medical Societies of Hong Kong; President: Dr. Raymond See-kit LO; Venue: Run Run Shaw Hall, The Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong	Ms. Eva TSANG Tel: 2527 8898
	8:00 pm HKMA Annual Ball 2014 Organiser: The Hong Kong Medical Association; Chairman: Dr. CHAN Yee Shing, Alvin; Venue: Grand Ballroom, Conrad Hong Kong, Pacific Place, 88 Queensway, Hong Kong	Ms. Candy YUEN Tel: 2527 8285



Rental Fees of Meeting Room and Facilities at The Federation of Medical Societies of Hong Kong (Effective from October 2009)

Venue or Meeting Facilities	Member Society (Hourly Rate HK\$)			Non-Member Society (Hourly Rate HK\$)		
	Peak Hour	Non-Peak Hour	All day Sats, Suns & Public Holidays	Peak Hour	Non-Peak Hour	All day Sats, Suns & Public Holidays
Multifunction Room I (Max 15 persons)	150.00	105.00	225.00	250.00	175.00	375.00
Council Chamber (Max 20 persons)	240.00	168.00	360.00	400.00	280.00	600.00
Lecture Hall (Max 100 persons)	300.00	210.00	450.00	500.00	350.00	750.00
Non-Peak Hour: 9:30am - 5:30pm Peak Hour: 5:30pm - 10:30pm						
LCD Projector	500.00 per session					
Microphone System	50.00 per hour, minimum 2 hours					



HKFMS Charity Project for Bereaved Children - Drum Circle

"Drum Circle" Fun Day was co-organised by the HKFMS Foundation and Inspire Movement Association on 5 Oct, 2014 at the Wan Chan Southern Stadium. This event aimed to provide an opportunity for bereaved children and families to enjoy the percussion music, as well as to better support each other with fellow children of society. We were glad to invite Mr Channon LIU, an experienced Drum Circle Instructor to lead the event. We would like to thank our partners, Tom Lee Music Foundation & Tom Lee Music Co. Ltd for promoting the event. This event is part of the ongoing charity projects for bereaved children supported by the HKFMS Foundation. The HKFMS Foundation looks forward to collaborate further with various partners to contribute to the society.



"Contemporary Management of Benign Prostatic Hyperplasia" Symposium

On 9 October 2014, a lunch symposium on Contemporary Management of Benign Prostatic Hyperplasia was co-organised by the Federation and Hong Kong Society of Practising Urologists. It was held at the World Trade Centre Club, Hong Kong, Causeway Bay. The symposium was well attended by doctors, nurses and allied health professionals.

The Federation was privileged to have Dr Steve Wai-hee CHAN, specialist in Urology as our speaker; with Dr Chi-wai MAN, Consultant Urologist & Chief Service of the Department of Surgery, Tuen Mun Hospital & Pok Oi Hospital, as our chairman. Dr CHAN analysed BPH pathophysiology and symptoms, demonstrated assessments and shared different management case studies. We would like to thank the generous support from Eli Lilly for sponsoring this event.



Federation visit to Shenzhen

The Federation organised a study group to visit Shenzhen at the weekend 18 – 19 October 2014. Dr Raymond LO, President of the Federation of Medical Societies of Hong Kong (FMSHK), led the group to visit the Hong Kong University – Shenzhen Hospital, 華大基因研究所 and stayed the evening at 深圳紫荊山莊. For the Sunday morning, 郭正林教授 from the SUN YAT-SEN UNIVERSITY, 現任中央政府駐港聯絡辦深圳培訓調研中心副主任, was invited to deliver a talk on the topic 珠三角城市與區域競爭力. Over 30 members and friends of the Federation joined this visit, and we would like to give our heartfelt thanks to the Liaison Office of the Central People's Government in the Hong Kong SAR to assist in co-coordinating this Shenzhen visit.





Office visit from the group of Shenzhen Hospital

Twenty health care professionals working in Shenzhen Hospitals attended a programme named “公立醫院監管專題研究” in Hong Kong organised by the School of Continuing and Professional Studies, The Chinese University of Hong Kong. The group visited the office of the Federation of Medical Societies of Hong Kong on 24 September 2014 in the morning. A talk on “Hospital Accreditation and Clinical Governance” was arranged and it was our pleasure to have invited Ms Bonnie Wong, Cluster Manager, Quality & Safety Department at the Tuen Mun Hospital and Ms Kamdy Ho as the speakers. There were a lot of questions raised and sharing on hospital quality auditing in hospitals both in the Mainland as well as Hong Kong.



Central & Western District Health Festival 2014/15

The annual Central and Western Health Festival, organised by the Central and Western District Council, was held successfully on 1-2 November 2014 at the Sheung Wan Sports Centre. Same as in past few years, the HKFMS Foundation Limited continued to support this event and was one of the co-organisers. This year, 4 health talks and 2 health booths were organised, composing of dental checks, eye test and games for the citizens. Over 1000 citizens visited our booths and joined the health checkup. We would like to express our sincere thanks to the following speakers and member societies, namely Dr Wai-man HUNG, Dr Kingsley CHAN, Dr Michelle CHAN and Mr Man-hei CHEUNG, the Hong Kong Society of Professional Optometrists, the Hong Kong Occupational Therapy Association and the Hong Kong Clinical Psychologists Association. In addition, we would like to also thank the following sponsors for their gifts and support: Oral-B, Alcon, Topcon Beijing (H.K) Limited and Mekim Limited.







Answers to Radiology Quiz

1. AXR- dilated small bowel loops

CT- a small bowel loop is noted superficial to L obturator externus and deep and inferior to L pectineus muscle. Small bowel loops proximal to this level are dilated.

2. Left obturator hernia.

3. This is a surgical emergency. This patient would need an urgent referral to the surgeons for decompression as the herniated bowel loop is at risk of strangulation.

An obturator hernia is a rare type of abdominal hernia, and can be clinically very difficult to diagnose. Typically obturator hernias occur in elderly women or patients with chronically raised intra-abdominal pressure (e.g. ascites, COPD, chronic cough). In general obturator hernias are asymptomatic unless they compress the obturator nerve : Howship-Romberg sign (only present in approximately half of cases) or when they contain bowel which incarcerates / obstructs / strangulates. Treatment involves surgery and repair of the hernial orifice.

Reference: Radiopaedia

Dr Charlotte KWONG

Department of Radiology, Queen Mary Hospital

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Security • Stability • Safety



Proven Evidence in BP Reduction and Stroke Prevention¹

Reference 1. Dahlof B, Sever PS, Poulsen NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet*. 2005;366:895-906.

NORVASCTM ABBREVIATED PACKAGE INSERT

TRADE NAME: Norvasc[®] **PRESENTATION:** 5mg tablet x 30's and 10mg tablet x 30's **INDICATIONS:** First line treatment of hypertension and first line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. **DOSAGE: Adults:** Initially 5mg once daily. Max: 10mg. Children (6-17 years): 2.5mg to 5mg once daily. **CONTRAINDICATIONS:** Known sensitivity to dihydropyridines, amlodipine, or any of the inert ingredients. **WARNINGS & PRECAUTIONS:** Patients with heart failure or impaired hepatic function. **INTERACTIONS:** None known. **PREGNANCY AND LACTATION:** Pregnancy Category C. Safety of amlodipine in lactation has not been established. **COMMON SIDE EFFECTS:** Flushing, fatigue, edema, dizziness, headache, abdominal pain, nausea, palpitations, somnolence. Children (6-17 years): headache, asthenia, dizziness, abdominal pain, vasodilatation and epistaxis. Reference: HK PI (version date Jan2008) Date of preparation: MAR2011 Identifier number: NORV0311 FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

"IN DOCTORS WE TRUST"



Most Taken and Recommended Statin by HK Physicians¹

According to 2013 ACC/AHA Guideline, statin therapy should focus on ASCVD risk reduction.²

MIRACL ³	SPARCL ⁴	TNT ⁵	ASCOT-LLA ⁶	CARDS ⁷	ARMYDA ⁸	PROVE-IT ⁹	IDEAL ¹⁰	GREACE ¹¹
✓	✓	✓	✓	✓	✓	✓	✓	✓

Proven to reduce CV events by up to 50% in multiple major CV outcomes trials.³⁻¹¹

- Efficacious LDL-C lowering^{12,13}
- Proven CV outcomes evidence from landmark trials³⁻¹¹
- NO dosage adjustment in patients* with renal impairment^{12,14}

*excluding kidney transplant patients



References 1. Ahead Research Consultants. "HCP's Statin Preference Research Report", 2013 n=120 physicians. 2. 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. American Heart Association, Circulation, 2013;127:2095-2478. 3. Schwartz GG, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes - the MIRACL Study: A randomized controlled trial. JAMA 2001;285(13):1711-1718. 4. Amarenco P et al. High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL). N Engl J Med 2006;355(6):549-559. 5. LaRosa JC, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med 2005;352:1425-35. 6. Sever PS, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-Lipid): A multicentre randomised controlled trial. Lancet 2003;361:1149-58. 7. Colhoun HM, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685-93. 8. Di Sciascio G, et al. Efficacy of Atorvastatin in Patients on Chronic Statin Therapy Undergoing Percutaneous Coronary Intervention: Results of the ARMYDA-HECAPITURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. JACC 2005;46(15):553-563. 9. Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2002;347(14):957-65. 10. Pedersen TR, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the DEAL Study, a randomized controlled trial. JAMA 2005;294(19):2437-45. 11. Athyros V, et al. Treatment with Atorvastatin in the National Cholesterol Education Program (Adult) Care in Secondary Coronary Heart Disease Prevention. The GREACE Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study. Curr Med Res Opin 2002;18:220-8. 12. Lipitor® (atorvastatin) Prescribing Information, Pfizer Corporation Hong Kong Limited, Version September 2011. 13. Law MR et al. BMJ 2003;326:1423-1427. 14. KDOQI Clinical Practice Guideline For Diabetes and CKD, 2012 Update. Am J Kidney Dis 2012;60(5):850-886.

LIPITOR APPROVED PACKAGE INSERT 1. TRADE NAME: LIPITOR. 2. PRESENTATION: The tablets for oral administration contain atorvastatin calcium equivalent to 10, 20, 40 or 80 mg atorvastatin. **3. INDICATIONS:** Adjunct to diet for the treatment of patients with elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia), combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb), elevated serum lipoprotein levels (Fredrickson Type IV), and for patients with dyslipoproteinemia (Fredrickson Type III) who do not respond adequately to diet. For the reduction of total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia when response to diet and other non-pharmacological measures are inadequate. Reduce the risk of myocardial infarction, stroke, revascularization procedures and angina in adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease. Reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension. Reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF and angina in patients with clinically evident coronary heart disease. Atorvastatin is also indicated as an adjunct to reduce total-C, LDL-C, and apoB levels in boys and postmenarcheal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL, or b. LDL-C remains ≥ 160 mg/dL, and there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patient. **4. DOSAGE:** The recommended starting dose of Lipitor is 10 or 20mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40mg once daily. The dosage range is 10 to 80 mg once daily. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks, and dosage adjusted accordingly. **5. CONTRAINDICATIONS:** Hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal. Pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus. **6. WARNINGS & PRECAUTIONS:** As with other lipid-lowering agents of the same class, moderate ($>3\times$ upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve(s). Should an increase in ALT or AST of greater than three times the upper limit of normal persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Myalgia has been reported in atorvastatin-treated patients. **7. INTERACTIONS:** Cyclosporine, fibrinolytic derivatives, lipid-modifying doses of niacin or cyclosporine P450 3A4 inhibitors (e.g., erythromycin and azole antifungals), clarithromycin, protease inhibitors, diltiazem, hydroxyzine, itraconazole, grapefruit juice, inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin), antiacids, colestipol, diphenhydramine, oral contraceptives, tacrolimus, zidovudine. **8. PREGNANCY AND LACTATION:** Atorvastatin is contraindicated in pregnancy and while breast-feeding. **9. SIDE EFFECTS:** Nausea, dyspepsia, hyperglycemia, pharyngodynia, pain, epistaxis, rashes, diarrhea, dyspnea, influenza, arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling, liver function test abnormal, blood creatine phosphokinase increased. **Reference:** HKPI (SEP2011) Date of preparation: FEB2013 Identifier number: LPI0213 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**



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