Future Challenges in the Management of Inborn Errors of Metabolism

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Introduction

Thirty years ago, when the third edition of Stanbury's *The Metabolic Basis of Inherited Disease*, the encyclopedic textbook on inherited metabolic diseases was published, it consisted of a single, relatively modest volume. The eighth edition, renamed *The Metabolic and Molecular Bases of Inherited Disease*, edited by Scriver and colleagues and published in 2001, was over 4 times bigger and contained information on a vast number of new diseases, as well as new information on previously described inborn errors of metabolism. The virtual exponential expansion of the textbook is an accurate reflection of the expansion of the field of inherited metabolic diseases in general.

Not only has knowledge expanded at a formidable rate, as a result of research in laboratories and clinics around the world, advances in technology have made early diagnosis easier and the outcomes of treatment better. New treatments are emerging that are having a profound impact on outcomes. Children with diseases that were formerly invariably fatal are now surviving and thriving into adulthood, as healthy productive citizens. Despite these advances, significant barriers continue to exist to the optimum detection, diagnosis, and treatment of these disorders.

Expansion of Scope

One of the immediate challenges posed by advances in our understanding of inborn errors of metabolism is the rapid and massive increase in the scope of the field created by the identification of new diseases. The list of disorders of transport and intracellular compartmentation has been expanded by the discovery of conditions, such as cerebral creatine deficiency, occurring as a result of mutations in membrane transporters. The discovery of congenital disorders of glycosylation has sensitised us to the existence of an entire class of inherited disorders of biosynthesis. Advances in laboratory and imaging technology have also provided us with the tools to identify and diagnose an enormous number of defects in mitochondrial respiration, adding another entire class of diseases to the catalogue of inborn errors of metabolism causing disease in humans.

The discovery of new variants of previously described diseases has added further to the scope of inherited metabolic diseases. Late-onset variants of diseases formerly thought to occur only in infancy are an example of this phenomenon. Often the clinical features of the disease in older children or adults is dramatically different from that presenting in infancy. For example, classical infantile Tay-Sachs disease is a rapidly progressive disease characterised by severe psychomotor retardation, intractable seizures, blindness, the appearance of cherry-red spots in the retina, and early death. Individuals with some residual β-hexosaminidase A activity generally present later, in early adulthood, often with ataxia, suggesting a spinocerebellar syndrome, but without seizures, visual impairment, or dementia.

Some diseases, formerly regarded to be non-metabolic syndromes, have had to be re-classified as a result of the discovery that the underlying lesion is deficiency of a specific enzyme, receptor, or transport protein. Smith-Lemli-Opitz syndrome, which is characterised by multiple malformations, including dysmorphic facies, micocephaly, cleft palate (in some), syndactyly, cryptorchidism and hypospadias, is now known to be caused by deficiency of the enzyme, 7-dehydrocholesterol reductase, an enzyme involved in cholesterol biosynthesis. The possibility that the psychomotor retardation that is a prominent feature of the disease is the result of cholesterol deficiency has prompted a number of attempts to treat the disease by supplementing the diet with large amounts of cholesterol.

The identification of adults with late-onset variants of inherited metabolic diseases occurring more commonly in infants, along with the improved survival of children with treatable inborn errors of metabolism, has created a rapidly expanding cohort of 'new', adult patients, requiring a different approach to management than that employed in children.

Advances in Diagnosis

One of the most important recent advances in the management of inherited metabolic diseases has been the burgeoning application of molecular genetics to the specific diagnosis of disease and especially to the identification of carriers of recessive mutant genes in relatives of patients with inborn errors of metabolism. This has been facilitated by the development of laboratory techniques for rapidly and relatively inexpensively screening entire genes for disease-

causing mutations. Molecular genetic information must be interpreted with care, however. Not all sequence variations cause disease. Whether a specific sequence change is responsible for disease generally requires consultation with a specialist in clinical or molecular genetics.

The specific diagnosis of mitochondrial electron transport chain (ETC) defects, especially those caused by nuclear gene mutations, is still a formidable challenge, both for the clinician and for the diagnostic laboratory. Although the clinical course of the disease in a patient, along with some routine biochemistry, such as measurements of lactate in plasma and CSF, and neuro-imaging changes, may strongly support a diagnosis of a mitochondrial disorder, such as Leigh disease, biochemical confirmation of the diagnosis is still very difficult. Studies on cultured skin fibroblasts, and even on fresh muscle obtained by biopsy, are cumbersome and often inconclusive. When mutation analysis of known mtDNA mutations is also inconclusive, only a presumptive diagnosis is possible. And, of course, carrier detection and prenatal diagnosis are not feasible.

Screening

The introduction of tandem mass spectrometry (MS) for the analysis of amino acids and acylcarnitines in blood has revolutionised the approach to newborn screening for inherited metabolic disorders. Although the technique is extraordinarily sensitive, it does present some challenges. The laboratory operating costs of screening by tandem MS are comparable to the costs of many other screening procedures. However, the capital costs of the required equipment are high. The technology has also generated information on many newborns that is difficult to interpret, adding to the cost of follow-up diagnostic investigation of infants who turn out to be normal.

Treatment

Major advances in treatment of inherited metabolic diseases have emerged over the past 20 years, especially enzyme replacement therapy (ERT) of lysosomal storage diseases. On the other hand, treatment is very expensive, well beyond the resources of individual families, and alternative ways of paying for it are not uniformly available. Although ERT of diseases, such as Gaucher disease is safe and has been dramatically effective in the treatment of non-neurological disease, the application to neurodegenerative lysosomal diseases continues to be severely limited by the relative inaccessibility of the CNS to intravenously infused enzyme. How to breach the blood brain barrier is one of the most urgent challenges in the management of inherited metabolic disorders.

Although many would argue that the most effective and lasting approach to the treatment of inborn errors of metabolism would, theoretically, be by gene replacement or gene transfer therapy, this continues to be an elusive goal and one of the most challenging problems for the next generation of clinical scientists committed to discovering better ways to treat these diseases. So far, despite enormous investments in research and significant advances in molecular biology and gene transfer technology, no unambiguously successful gene transfer treatment for an inborn error of metabolism has been reported.

Barriers to Access

Despite the major advances in technology and knowledge that have been made over the past several years, the management of patients with inborn errors of metabolism continues to be compromised by serious barriers to access to care. One of these is directly within our own power to change—that is awareness among physicians of the presence of these disorders among our patients. Conferences like the International Workshop on Inborn Errors of Metabolism in Children held in Hong Kong in October 2002 are one way to raise awareness of inherited metabolic diseases in children and how to deal with them.

The cost of care and the necessary support systems to provide optimum care for children with inborn errors of metabolism also pose important barriers to access. These barriers are not likely to be overcome unless the public accepts the care of children in general, and those with inherited metabolic diseases in particular, as a high priority for public support. The first challenge in dealing with the health policy problem is to mobilise public opinion and focus on those values that make the care of children a public policy imperative. What must follow is the development of mechanisms for evaluating new technologies, especially those relating to screening and to the treatment of inherited metabolic diseases, to achieve the re-allocation of resources necessary to make them available to the people.

The assessment of the merits of a new technology or treatment often focuses, at least initially, on whether a

particular technology or treatment works—*can* it be done? This type of assessment usually involves major input by technical experts, including physicians, and rests on the ability to evaluate objectively specific expectations of a new laboratory test or a new therapy. It has become codified in 'evidence-based medicine', and it has become critically important in decision-making regarding health care resource allocation. However, public values also play a central role in the process—*should* it be done? This is a much more difficult area of public policy development, and it requires input from a much wider group of stakeholders, including the general public.

Concluding Remarks

Paediatricians are faced with a number of challenges directly related to the management of inborn errors of metabolism. Staying abreast of the rapid expansion of knowledge in this area, along with the emergence of new diagnostic and screening technologies, is a familiar, though daunting, task. Despite the advances in knowledge, however, there is a pressing need for the development of new and effective treatments for many inherited metabolic diseases, especially those affecting the brain. One of the most formidable and difficult challenges is the removal of barriers to access to existing diagnostic and treatment services. Facing the public policy challenge is generally unfamiliar territory for practicing paediatricians. However, it is one in which we must be prepared to participate in a more active way than in the past if the advances in medicine that are occurring now are to reach our patients in the future.

Public Health Approach of Inborn Errors of Metabolism in Hong Kong

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The commonest inherited metabolic disease in Hong Kong is glucose-6-phosphate dehydrogenase (G6PD) deficiency. When a disease is of significant incidence and severity, the public health approach would be considered for its prevention and management. In Hong Kong, G6PD deficiency was recognised as one such condition that required massive screening and early intervention. A combined neonatal screening programme for G6PD deficiency and congenital hypothyroidism (CHT) was started in Hong Kong by the Department of Health (DH) since 1984. The screening system included activities in public education, sampling, laboratory assays, follow up intervention and evaluation. As a public health programme, it was provided free of charge on a totally voluntary basis. Although all newborns in Hong Kong were entitled to this service, only about 70% of life birth had their blood samples directed to the central neonatal screening laboratory under this programme, the remaining 30% received screening from laboratories in private hospitals. Overall, more than 99% of all newborns in Hong Kong received screening for these disorders. Cord blood was used universally as the screening sample for both conditions. The decision of employing cord blood, instead of filter paper blood spot, was based on two reasons. Firstly, it was considered important that any deficiency of this enzyme in a newborn need be notified within the first couple of days for effective counselling and intervention. The use of cord blood certainly offered distinct advantage. Secondly, transport of these samples was not a problem in a geographically compact place like Hong Kong. Screening for G6PD enzyme activity was performed by colorimetric assay. Up to the end of December 2001, a total of 679,241 neonates had been screened in the public hospitals. It was found that 4.53% of the males and 0.32% of the females were affected. Compared with 1970s, there was a tremendous decrease in the morbidity and mortality resulting from hyper-bilirubinaemia due to G6PD deficiency. There are occasional cases of mishap as a result of failure to inform individual families of G6PD deficiency during the long holidays. Counselling for this condition was normally conducted by phone by genetic counselors, and this method had been shown to be effective.