Neurodegenerative diseases in children

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The detection of neurodegenerative and neurometabolic diseases in children relies on a high index of suspicion as most will present as common paediatric problems such as recurrent vomiting, feeding problem, failure to thrive, sepsis, or developmental delay. Alternatively, children may present with an acute encephalopathy or with a chronic progressive encephalopathy. Clinical clues suggestive of neurometabolic disorders include encephalopathic features such as microcephaly, macrocephaly, developmental regression, developmental arrest, change in sensorium, seizures, hypotonia, hypertonia, abnormal eye signs; also extrapyramidal or cerebellar signs and systemic features like abnormal respiration, hepatosplenomegaly, abnormal hair, liver dysfunction, renal tubular dysfunction, cardiomyopathy, and feeding difficulties or growth problems. Initial screening includes tests for acidosis, ketosis, hyperlacticemia, and hyperammonemia. Further investigations should include amino acid chromatography, assays of organic acids, specific enzyme assay of white cell or fibroblast culture, and histopathology of cell and tissue biopsy (white blood cell, skin, muscle, conjunctiva, bone marrow, liver, rectum, or brain). The correct diagnosis holds implications for targeted therapeutic intervention, genetic counselling, and possibly, prenatal diagnosis.

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Introduction

Neurodegenerative disease (ND) is rare in children. The approach relies on a high index of suspicion and the collation of all relevant clinical data so that the correct investigations are made. Making a correct diagnosis holds significance for genetic counselling, and hopefully, the prevention of diseases.1

The detection of ND is often hampered by the failure to recognise that which usually presents as a common paediatric problem (sepsis, recurrent vomiting, feeding problem, failure to thrive, intrauterine growth retardation, developmental delay). In addition, children may present with unexplained mental retardation, cerebral palsy, or epilepsy.2 A well taken history is an essential prerequisite to a thorough investigation.

The child neurologist faced with a child with a progressive encephalopathic picture, has to decide if the involvement is restricted to the central nervous system solely or if there is multisystem involvement; whether the disease is limited to the central nervous system only, or the peripheral nerves; and whether there is grey matter or white matter involvement.

Presenting features of neurodegenerative diseases

The presenting features of children with ND can be acute, fulminating, and rapidly progressive, or subtle and slowly progressive. A time course and sequential neurological and developmental assessments are needed to distinguish a static encephalopathy from a slowly progressive degenerative disease. Of course, treatable conditions such as space-occupying lesions, infections, and metabolic disorders need to be excluded.

Neurodegenerative diseases that present with acute encephalopathy include maple syrup urine disease, organic acidurias, lactic acidosis, urea cycle disorders,
and nonketotic hyperglycemia. Routine studies include the determination of blood gas, ketones, lactate, and ammonia and special studies such as urine analysis for the presence of organic acids and amino acids.

Neurodegenerative disease that appears as a chronic progressive encephalopathy includes sphingolipidosis, mucopolysaccharidosis, glycoprotein degradation disorders, peroxisomal disorders, fatty acid oxidation disorders, and neuronal ceroid lipofuscinosis. Routine studies include urine analysis for mucopolysaccharides and oligosaccharides. Special studies include looking for inclusion bodies in lymphocytes, very long chain fatty acids, and lysosomal enzymes.

The definitive diagnosis for both categories rests on enzyme assay in white blood cells, skin fibroblasts, and tissue.

**Neurodegenerative disease with a metabolic basis**

The clinical features that suggest a ND with a metabolic cause are mainly neurological and systemic ones. Neurological features include frequent epileptic seizures (especially infantile spasm, myoclonus), a gradual development of spasticity, dementia, developmental regression, visual or auditory deterioration, extrapyramidal symptoms, cerebellar symptoms, microcephaly, macrocephaly, speech problems, or psychiatric symptoms.

Abnormal eye examination includes optic atrophy, retinal depigmentation, abnormal eye movement, ocular motor dyspraxia, nystagmus, tapetoretinal degeneration, and cherry red spots.

Suggestive systemic features include intrauterine growth retardation, failure to thrive, poor suckling, weak cry, repeated vomiting, susceptibility to infection, seborrhea, alopecia, abnormal hair, abnormal urine odour, renal tubular degeneration, bone marrow depression, cardiomyopathy, hepatomegaly, hepatosplenomegaly, or typical features of gargoylism.

The pathogenesis of ND is related to the synthesis, metabolism, transport, and storage of biochemical compounds. Among the 300 inborn errors of metabolism, the central nervous system is involved in about one-third of cases. This includes organic acidurias, aminoacidurias, lysosomal storage disorders (sphingolipidosis, mucopolysaccharidoses, glycoprotein degradation disorders), fatty acid oxidation disorders, congenital lactic acidosis, peroxisomal disorders, urea cycle disorders, and neuronal ceroid lipofuscinosis.

Neurometabolic disorders can present either with acute encephalopathy or as chronic progressive encephalopathy. With the former, the age of onset is usually in the neonatal or early infancy period, with predominantly grey matter involvement. The clinical features include cognitive impairment, seizures, visual impairment, vomiting, lethargy, coma, and abnormal respirations.

With chronic progressive encephalopathy, the onset is usually in infancy, childhood, or adolescence, with predominantly white matter involvement. Features include spasticity, ataxia, hyporeflexia, liver dysfunction, cardiomyopathy, and weakness.

**Defining neurometabolic diseases**

Neurometabolic diseases can be defined according to clinical features based on anatomic location (grey or white matter involvement); symptoms present (intoxications and energy deficiencies); age of onset; and neurological manifestations (acute or chronic and progressive encephalopathies).

**Clinical features based on anatomic location**

If the grey matter is affected, the child presents with abnormalities of cognition (mental retardation), vision, hearing, and seizures. If the white matter is affected, there may be loss of motor skills, spasticity, or ataxia. These distinguishing features are useful only in the early stages of the disease, as both grey and white matters are involved at a later stage as the disease progresses.

**Symptoms—intoxications and energy deficiencies**

Intoxications result from accumulation of toxic metabolites proximal to the blockage of metabolic pathway. This includes organic acidurias, aminoacidurias, urea cycle defects, galactosemia, fructoseemia, and tyrosinemia.

Energy deficiencies are caused by the impaired production or use of energy due to defects in the liver, myocardium, muscle, or brain. This includes glycoenzyme storage disorders, congenital lactic acidosis, fatty acid oxidation defects, mitochondrial disorders, and peroxisomal disorders.

**Age of onset**

There can be various ages of onset of the illness. This can be neonatal (less than one month), early infantile
Table 1. Studies for the detection of neurometabolic disorders—acute encephalopathy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Routine studies</th>
<th>Special studies</th>
<th>Enzyme studies</th>
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<tr>
<td></td>
<td>Blood gas</td>
<td>Ketones</td>
<td>Lactic acid</td>
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<tr>
<td>Maple syrup urine disease</td>
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<td>Organic aciduria</td>
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<td>Lactic acidosis</td>
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<td>Urea cycle disorder</td>
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<td>Nonketotic hyperglycinemia</td>
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(1-12 months), late infantile (1-4 years), and late childhood (juvenile, 5-15 years). Some diseases can present at different ages with differing degrees of severity. The age of onset is important for deciding the clinical approach to various categories of ND.

Neonatal
Diseases with onset at birth include generalised GM₁ type I gangliosidosis, type I glycogen storage disease, neonatal adrenoleukodystrophy, mucolipidosis II, and Alexander’s disease.

Early infantile
Disorders with onset at one to three weeks include galactosemia and maple syrup urine disease. Onset at one to three months include type II glycogen storage disease (Pompe’s) and the infantile type of neuronal ceroid lipofuscinosis. Diseases with later onset at three to six months include Gaucher’s disease, Tay-Sachs disease, Krabbe’s disease, Niemann-Pick disease (type A), phenylketonuria, and Canavan’s disease; those with onset at three to twelve months include the Lesch-Nyhan syndrome and Pelizaeus-Merzbacher disease.

Late infantile
Diseases with onset at six months to two years include adrenoleukodystrophy and juvenile GM₁ gangliosidosis type II; onset at six months to four years includes homocystinuria. Disease onset at one to three years includes Hurler’s syndrome, metachromatic leukodystrophy, neuroaxonal dystrophy, and Leigh’s disease. Onset at one to six years includes type C Niemann-Pick disease, whereas later onset (at 2-5 years) includes the late infantile type of neuronal ceroid lipofuscinosis. Onset at two to six years includes Hunter’s syndrome and GM₁ type III gangliosidosis.

Late childhood
Disease onset at four to eight years includes the juvenile form of neuronal ceroid lipofuscinosis and Sanfilippo syndrome; at five to ten years it includes adrenoleukodystrophy and Huntington’s chorea. Onset at eight to 15 years includes Lafora body disease and at 10 to 12 years, type D Niemann-Pick disease. Onset at five to 20 years includes juvenile metachromatic leukodystrophy, Gaucher’s disease type III (juvenile form), mucolipidosis I, and Hallervorden-Spatz syndrome.

Neurological manifestations
Acute encephalopathy usually presents early in life with recurrent vomiting, poor feeding, lethargy, and dehydration. The grey matter is affected initially, and represents an intoxication or toxic encephalopathy.

Chronic or progressive encephalopathy usually presents in later childhood with spastic ataxia, dementia, visual, and hearing loss. Other organs such as the liver, heart, muscle, and kidney are commonly involved. The white matter is affected initially, but ultimately both grey and white matter are involved. This can be due to intoxication and/or energy deficiency.

Investigations for neurodegenerative disease

General investigations
General initial laboratory studies include blood analysis for the following: complete blood count, glucose, calcium, anion gap, electrolytes, ammonia, aminotransferases, lactic acid, pyruvic acid, uric acid, ketones (β-hydroxybutyric acid and acetocacetic acid). Urine analysis is performed for odour, pH, ketones, and to screen for metabolites.

Positive urine screening for metabolic disorders includes: dinitrophenylhydrazine (phenylketonuria or other aminoaciduria), ferric chloride and dinitrophenylhydrazine (organic aciduria), reducing substance...
(galactosemia), nitroprusside (homocystinuria), and cetyl trimethylammonium bromide or Berry spot (mucopolysaccharidosis).

Preliminary investigations include looking for vacoulation of the lymphocytes (gangliosidosis, glycoprotein degradation disorders), raised acid phosphatase (Gaucher’s disease), and metachromatic granules in the urine (metachromatic leukodystrophy). Raised serum lactate occurs in mitochondrial disorders and in Alpers’ disease. Hyperammonemia occurs with some NDs such as carbamyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency, or organic aciduria.

**Other investigations**
Lactate and pyruvate levels are raised in mitochondrial disorders and the protein level is raised in leukodystrophy and other demyelinating disorders. Children with dysmorphic features need chromosomal studies. Chromosomal analysis has been found to be associated with certain disorders—chromosomes 1 and 16 in neuronal ceroid lipofuscinosis and chromosome 21 in progressive myoclonus epilepsy (Lafora disease).

**Neurophysiological investigations**

**Electroencephalogram**
With diffuse cortical and subcortical grey matter disease there are bilaterally synchronous paroxysmal discharges. In white matter disease, the electroencephalogram (EEG) may show continuous non-paroxysmal slow wave activity. In diseases involving both the grey and white matter, there will be bilaterally synchronous paroxysmal discharges and a marked increase in slow wave activity.

In infantile neuronal ceroid lipofuscinosis, there is a progressive reduction in amplitude after infancy, and high voltage complexes are induced posteriorly with a slow rate of photic stimulation. In infantile neuroaxonal dystrophy, diffuse fast (beta) waves of moderate amplitude develop after two years of age. In progressive neuronal degeneration of childhood (Alpers’ disease), multiple spikes superimposed on lateralised large slow waves are found, and this predicts later liver involvement.

**Electroretinogram**
The electroretinogram (ERG) provides information about the retina by averaging the response to repeated light flashes, both the photopic and scotopic (dark-adapted) response. Low or extinguished ERGs are found in those with congenital low vision (peroxisomopathies) and late onset of low vision (neuronal ceroid lipofuscinosis, mitochondrial cytopathy,

<p>| Table 2. Studies for the detection of neurometabolic disorders—chronic progressive encephalopathy |</p>
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Enzyme studies</th>
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<td>Fibroblasts</td>
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<td>White blood cells</td>
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<th>Special studies</th>
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<td>Inclusion bodies</td>
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<td>Very long chain fatty acids</td>
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<th>Routine studies</th>
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<td>Urine mucopolysaccharides</td>
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<td>Urine oligosaccharides</td>
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<table>
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<th>Disorder</th>
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<tr>
<td>Sphingolipidosis</td>
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<td>Macropolyascharidosis</td>
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<td>Glycoprotein degradation disorder</td>
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<tr>
<td>Fatty acid oxidation disorder</td>
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<td>Peroxisomal disorder</td>
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<tr>
<td>Neuronal ceroid lipofuscinosis</td>
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Refsum’s disease, Hunter’s syndrome, and mucolipidosis type IV).

Visual evoked potential
In children, it is useful to record the ERG, visual evoked potential (VEP), and EEG to document the site and type of lesion. In disorders of the peripheral retina (e.g. early stage of retinitis pigmentosa), the ERG may be absent but the VEP may be normal. If there is diffuse involvement of the retina, including the macula and the periphery, both the ERG and VEP will be absent. If only the retinal ganglion cells degenerate (e.g. infantile GM1 gangliosidosis), the ERG is normal and the VEP may be absent.

The VEP is abnormal in lesions of the anterior visual pathway, optic nerves, and optic chiasm. In axonal lesions (optic hypoplasia, compressive lesion of the optic nerve), the amplitude of P100 is decreased and the VEP waveform is distorted. With demyelinating lesions (optic neuritis, leukodystrophy), the latency of P100 is increased and the amplitude and waveform are normal.

Both the VEP and EEG are abnormal in lesions of the posterior visual pathways; the EEG may show occipital spikes in periventricular leukomalacia. Lesions in the visual cortex may show flattening of the EEG with normal VEP.

In neuronal ceroid lipofuscinosis, serial ERG, VEP, and EEG are helpful in making the diagnosis. In the infantile form, these three become smaller until they are either extinguished or flattened. In the late infantile form, the ERG is extinguished early but the VEP is enlarged, with giant VEP seen in the EEG at 2-5 Hz photic stimulation. In the juvenile form, the ERG disappears early and later on the VEP may show a reduction in amplitude and the EEG is abnormal.

Brainstem auditory evoked potential
This assesses the integrity of the auditory nerve (sensorineural deafness) and the central auditory pathway (brainstem). Increased interpeak latency of waves I-V may be found in a demyelinating disorder and a reduction of wave V amplitude (i.e. decreased wave V: wave I ratio) may be found in an axonal lesion.

Somatosensory evoked potential
This assesses the pathway from the peripheral nerve through the posterior column to the somatosensory cortex.

Nerve conduction study
Motor and sensory nerve conduction study differentiates between demyelinating and axonal neuropathies. The nerve conduction velocity is markedly decreased in demyelinating neuropathy and the amplitude of the motor or sensory action potential is decreased in axonal neuropathy.

Electromyogram
This is useful for differentiating denervation/neurogenic changes from myopathic changes. Abnormal spontaneous activity (e.g. fibrillations) are found in denervation but also in some myopathies. Abnormality on exertional activity is more useful for differentiating the lesions. In neurogenic lesion, the interference pattern is reduced, whereas the duration of the motor unit potential is long and the amplitude is high. In myopathy, the interference pattern is full and the motor unit potential is of short duration and low amplitude.

Neuroradiology
Specific skeletal changes are found in mucopolysaccharidosis, mucolipidoses, gangliosidosis, and homocystinuria. A computed tomography (CT) scan of the brain will show any intracranial calcification and non-specific changes of cortical atrophy. White matter hypodensities can be found in leukodystrophies, aminoacidopathies (maple syrup urine disease, phenylketonuria), and in peroxisomopathy (Zellweger syndrome). Striatal hypodensities are found in Leigh’s disease, mitochondrial disorders, and in organic aciduria (methylmalonic aciduria).

A magnetic resonance image (MRI) scan of the brain is more sensitive than a CT scan in defining the extent of lesions in demyelinating and dysmyelinating disorders. The sensitivity of an MRI scan in detecting these disorders is equal to a CT scan.

Single photon emission computed tomography (SPECT) provides information on the cerebral blood flow in stroke, which can help to differentiate vascular from metabolic stroke in mitochondrial encephalopathy lactic acidosis and stroke. In contrast, the positron emission tomography (PET) scan provides information on the metabolism of the brain.

Making a definitive diagnosis
An enzyme assay of leukocytes or cultured skin fibroblast can assist in making a definitive diagnosis. Cells and tissues can also help in making the diagnosis in some disorders.
Vacuolated lymphocytes are found in mucolipidosis (very numerous and small), the juvenile type of neuronal ceroid lipofuscinosis (NCL) [few but larger], and in some lysosomal storage diseases (infantile type of GM, gangliosidosis, Niemann-Pick disease type A, mannosidosis, fucosidosis). Examination of the buffy coat under electronmicroscopy is useful in making a diagnosis of neuronal ceroid lipofuscinosis. Membrane-bound granular osmophilic deposits are found in infantile NCL, while curvilinear bodies are found in many lymphocytes in late infantile NCL. In infantile NCL, autofluorescence is detected under ultraviolet light.

In metachromatic leukodystrophy, toluidine blue staining of urine sediment can show the golden-yellow metachromatic material in renal epithelial cells and green birefringence of the renal epithelial cells are found in polarized light. In infantile neuronal ceroid lipofuscinosis, yellow autofluorescence is found with ultraviolet light.

Twisted hair (pili torti) is found in Menkes’ disease and arginosuccinic aciduria. Intermittent swollen breaks (trichorrhexis nodosa) may be found in Menkes’ disease, biotinidase deficiency, and arginosuccinic aciduria.

The conjunctiva is rich in nerve fibres. Curvilinear bodies are found in NCL. In mucolipidosis type IV, multilaminate bodies may be seen in epithelial and endothelial cells. In neuroaxonal dystrophy, dystrophic axons with spheroids may be found in the conjunctiva and skin.

The muscle in some mitochondrial encephalopathies shows the typical ragged red fibres with Gomori trichrome stain. Abnormalities of the succinic dehydrogenase reaction may suggest mitochondrial disease, even in the absence of ragged red fibres. The muscle fibres contain Periodic Acid Schiff and peroxidase-positive granules in Latafia body disease. In neuroaxonal dystrophy, the spheroids may be found in the intramuscular nerve. Biochemical study of the electron transport chain in mitochondrial disorders can be performed.

Biopsy of the peripheral nerves shows neuroaxonal spheroids in infantile neuroaxonal dystrophy. A brain biopsy may help in the diagnosis of demyelinating diseases (Alexander disease and Canavan’s disease). In neuroaxonal dystrophy, brain biopsy with esterase histochemistry may provide a definitive diagnosis in those with negative findings in skin, conjunctiva, or muscle biopsies.

In NCL, autofluorescence under ultraviolet light and electron microscopic findings provide a definitive diagnosis if other tissue examinations have been unrevealing. In peroxisomopathies, the liver biopsy may show a decrease in peroxisome numbers or enlarged peroxisomes with abnormal shapes. In progressive neuronal degeneration of childhood (Alpers’ disease), fatty infiltration or cirrhosis may be found.

Bone marrow aspiration may show the typical cells found in Gaucher’s disease and Niemann-Pick disease.

**Laboratory investigations for acute or progressive encephalopathies**

A summary of the laboratory approach to acute or progressive encephalopathy is illustrated in Tables 1 and 2. Despite exhaustive investigations, there still remain some neurodegenerative diseases where diagnosis is mainly a clinical one, to be confirmed, if possible, by postmortem tissue examination.

**Prototypes of inherited neurometabolic disorders**

Using the four laboratory parameters (acidosis, ketosis, lactate, and ammonia), NDS can be categorized into five subtypes: maple syrup urine disease (presence of ketosis without acidosis, with normal lactate and ammonia); organic acidurias (presence of acidosis and ketosis, with normal lactate and ammonia); congenital lactic acidosis (presence of acidosis, ketosis, and raised lactate, with normal ammonia); urea cycle disorders (absence of acidosis and ketosis, normal lactate, and hyperammonemia); and nonketotic hyperglycemia, sulphite oxidase, peroxisomal or disorders of the respiratory chain (absence of acidosis or ketosis, normal lactate, and ammonia).

**When to refer?**

One of the most common referrals to a general paediatrician is of a child with developmental delay. When should the general paediatrician refer the child to a child neurologist for further evaluation? The general paediatrician should determine whether the delay is global or specific in nature. The first question to be asked is: is it really only developmental delay or is it developmental regression? If there are features suggestive of developmental arrest or developmental regression, the child should be referred to a child neurologist for further workup.
Treatment

Treatment of most NDs or neurometabolic diseases is mainly supportive. Dietary restriction is useful in certain diseases (phenylketonuria, maple syrup urine disease, adrenoleukodystrophy) and prenatal diagnosis is possible in some diseases. An assay of enzyme in cells can be obtained by chorionic villus sampling (8-12 weeks gestation) or amniotic fluid (14-16 weeks gestation).

New treatments

Bone marrow transplantation has been tried with various diseases, and has shown promising results when performed at a stage where irreparable brain damage has not occurred. This includes lysosomal storage diseases, mucopolysaccharidoses, Gaucher’s disease, metachromatic leukodystrophy, and adrenoleukodystrophy.1

Somatic gene therapy targeted at the central nervous system is still at the embryonic stage. Neuronal transplants using foetal brain tissue have been conducted, but immunological and ethical issues are matters of concern.

Current situation in Hong Kong

The facilities for complete workup for most NDs are not currently available in Hong Kong. Routine investigations that are available include: uric acid, acid phosphatase, bile acids, serum lactate and pyruvate, urine analysis for metabolic screening and for amino acid chromatography. Special arrangements for other tests are also available, including serum very long chain fatty acids, urine for organic acids, electron microscopy of lymphocytes/neutrophils and assay for lactate and pyruvate in cerebrospinal fluid.

Specific enzyme assays that are available include arylsulphatase A and B, hexosaminidase A and B, and galactose-1-phosphate uridyl transferase. Available neurophysiological studies include: VEP, brainstem auditory evoked potential, somatosensory evoked potential, ERG, motor and sensory nerve conduction study, electromyography, and EEG with photic stimulation.

Neuoradiological investigations available locally include CAT scan, MRI scan, and SPECT scan. Tissue analysis includes needle muscle biopsy for histochemistry and electron microscopy, skin biopsy, conjunctival biopsy, brain biopsy, rectal biopsy, and bone marrow examination. Neuodegenerative disease has rarely been diagnosed in Hong Kong due to the lack of laboratory support. Most of the enzyme assays are not available in Hong Kong and have to be performed by overseas laboratories.

Summary

Neuodegenerative and neurometabolic diseases are rarely seen in the general paediatric practice. A heightened awareness of these disorders in any child presenting with unexplained common childhood problems, especially those with associated encephalopathic or systemic features, is essential. The improvement in diagnostic yield through simple screening laboratory procedures, and the establishment of a collaborative, interdisciplinary diagnostic centre within Hong Kong would certainly help diagnose many of the unexplained childhood NDs.

References