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BRAINCHILD

The Official Publication of HKCNDP
Diagnostic Challenges in Child Neurology

香港兒童腦科及體智發展學會
The Hong Kong Society of Child Neurology and Developmental Paediatrics

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DIAGNOSTIC CHALLENGES IN CHILD NEUROLOGY

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BRAINCHILD – NOVEMBER 2005 ISSUE

Message from the President

The WHO definition of *health* evolves over the past five decades from "a state of freedom from diseases" to the "state of physical, mental, psychological, spiritual and social well being" and now the "ability to attain one's potential in life". This illustrates the concept of health consequent to the good control of infectious and genetic diseases, effective medical care of pregnancy and child delivery, excellent paediatric care in decreasing birth asphyxia and complication of prematurity as well as improvement of environmental health which we have just started to promote. We are now at a better stage of child survival and can afford to focus on the quality of life. Childhood mental health thus stands out as a subject of concern amongst professionals. The Hong Kong Joint Committee on Child Health formed by the Hong Kong Paediatric Society, the Department of Health of the Hong Kong SAR Government and the Hospital Authority has as far back as 2001 created a Task Force on Mental Health Services for Children in Hong Kong headed by Dr Ernest Luk (child psychiatrist) and Dr William Wong (paediatrician) to study mental health problems in this locality. Through the dedicated work of the Task Force, two notable products were achieved: "*The Survey on Mental Health Problems for Children in Hong Kong*" (which revealed major problems including ADHD, Autistic Spectrum Disorders, Specific Learning Disabilities, Behaviour Disorders, and others amongst our children) and a "*Model for Child Mental Heath Services in Hong Kong*". The Model proposed to divide childhood mental health services into four levels of care by different professionals (Level I by primary care paediatricians, Level II by developmental paediatricians, Level III by psychiatrists, and Level IV by child psychiatrists). The model sets a good prototype for further study and alerts all professionals to line up themselves to make the services effective, efficient, seamless and integrative. Active measures are being undertaken to update paediatricians to take up this challenging and yet important aspect in child health.

2005 is a busy year for the Hong Kong Society of Child Neurology and Developmental Paediatrics because we have outstanding achievements in the area of behaviour paediatrics. We have successfully convinced the Rehabilitation Advisory Council of Hong Kong to include Specific Learning Disabilities (SLD) into the Rehabilitation Planning Programme (RPP) and henceforth SLD is officially taken as a disability in Hong Kong. Such recognition by the HKSAR Government enable individuals with SLD to have access to accommodation, remediation, compensation, and resources provisions at health, medical education, transport, housing and other sectors which are heavily involved in the care of such individual. The other area of triumph is our joint attempt in successfully arousing the awareness of Attention Deficit Hyperactivity Disorders (ADHD) amongst members of the Rehabilitation Advisory Council which sets solid foundation for future effort to have this disability included into the RPP as well. Another endeavour of our Society is to strive for the implementation of the *WHO International Classification of Function (ICF) 2002* based on *Body Structure and Function, Activity, and Participation* in Hong Kong replacing the old *WHO Classification of Impairments, Disabilities and Handicap (ICIDH*

1980) which is outdated and obsolete in most of the developed world. We need coordinated and concerted effort to have this modern concept realized in Hong Kong so as to safeguard our good work in Rehabilitation which is world famous for being pioneering and caring for our children with special needs.

In order to continue our effort, the Society resolves to set up a Working Party on ADHD to coordinate activities within the subject with objectives to assess local incidence, explore magnitude of the problem, initiate advocacy work, set up strategic plans to tackle the problem, and educate local professionals (paediatricians, developmental paediatricians, clinical psychologists, nurses, school teachers and others) on their understanding of the subject. We have a series of activities designated to update professionals on the subject. This started with the innovative lecture jointly hosted by the Hong Kong Society of Child Neurology and Developmental Paediatrics together with the reputable organization FOCUS (Focus On Children's Understanding in Schools) on "Advanced Assessment and Treatment of ADHD" by Dr Thomas Brown Ph. D., Clinical Psychologist from Yale Clinic for Attention and Related Disorders and world authority on the subject, held on 4th October 2005 in Queen Elizabeth Hospital. We have also designated ADHD as title for our Society's Neurodevelopmental Conference on 21st October 2005 and the theme for the 2006 Annual Scientific Meeting of our Society. We are confident that with the precious experience we learned from Specific Learning Disabilities and with the joint effort of all professionals concerned (paediatricians, child neurologists, developmental paediatricians, child psychiatrists, clinical psychologists, nurses, teachers, social workers and others), we should be able to improve our services for children and adolescents with ADHD so that they would not be unjustifiably punished as being naughty and disobedient at home and in school. We need all your contribution to make this into a success!

The current issue of *Brainchild* is devoted to "Some Diagnostic Challenges in Child Neurology" whereby we include good accounts on "Outcome of Inflicted Traumatic Brain Injury" followed by case reports on "A Young Girl with Biotinidase Deficiency Presented with Guillian-Barre-Like Syndrome and later with Ataxia and Alopecia", "An Infant with Intractable Seizures, Peculiar Facial Features and Retinal Abnormalities" and "Case Report: All that twitches is not tics nor epilepsy", The Issue concluded with journal review of interesting articles related to the subspecialties of child neurology and developmental paediatric. Dr Wu Shun Ping and article authors are to be commended for contributing these interesting papers which I am sure would provide useful professional information for clinicians in their daily practice.

I wish you all reading pleasure and best of health!

Dr Chok-wan CHAN
Editor-in-Chief, *Brainchild*
President, The Hong Kong Society of Child Neurology & Developmental Paediatrics

Clinical Features and Outcome of Inflicted Traumatic Brain Injury

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Introduction

Inflicted traumatic brain injury (iTBI) is an important and preventable cause of acquired neurological disabilities. This study aims as depicting the commonly seen patterns of iTBI and also their clinical outcome.

Method

This is a retrospective study of all patients admitted to the paediatric department of regional hospital who were diagnosed to have inflicted brain injury over a ten year period from January 1993 to December 2002. The subjects were identified by retrieving case records bearing the diagnosis of "shaken baby syndrome", "subdural haematoma" or "skull fracture". These clinical records were reviewed and the cause of the injury was determined from the clinical notes. All subjects had injuries that were not ascribable to accident, commonly because of the occurrence of specific patterns of injury that was not consistent with the account given, or there was a lack of an account thereof. The demographics and clinical features were collected for analysis.

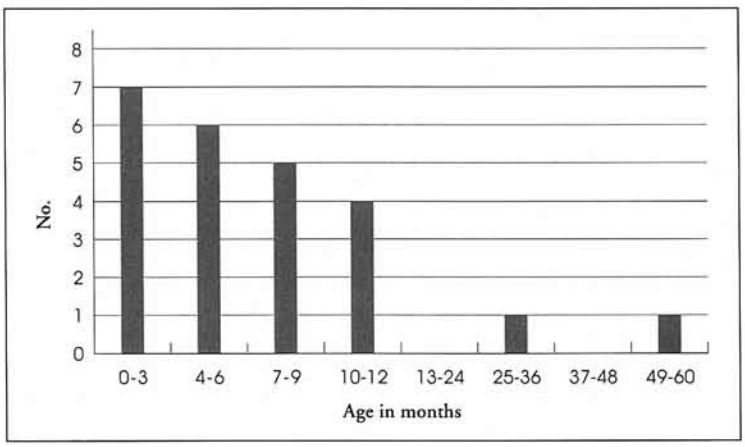
Statistical Method

Fisher's exact test is used for univariate analysis of categorical variables of clinical features and outcome. Significance level (p) of less than 0.05 is regarded as significant.

Results

Twenty four patients, fifteen male and nine female, were identified. All but two subjects were below 12 months old (figure 1).

Figure 1: Age at presentation of 24 patients with inflicted traumatic brain injury



The mechanisms of injury were compatible with shaking in 16 infants under one year old (67%), as evidenced by the absence of skull fracture or external injury and the occurrence of subdural haemorrhage, plus ancillary features of retinal haemorrhage, brain contusion and grip marks over the chest or shoulders in various combinations. Two had injuries compatible with impact (8%), suggested by skull fracture and epidural haematoma. For the remaining six (25%) the mechanism could not be determined.

Tonic seizure was the most common presenting symptom, present in 17 patients (70.8%). Ten patients (41.7%) presented with impaired consciousness and eight (33.3%) with lethargy. Retinal haemorrhage was present in 15 subjects (63%). Pallor, a very common feature in babies who were shaken, was only reported in two babies (8.3%). Less frequently reported symptoms included vomiting in four (6.7%) and difficulty in breathing in one (4.2%).

Regarding the injury sustained by the victims, subdural haemorrhage was found in 22 of the 24 (92%). Extensive subdural haemorrhages, defined by coverage of more than one quarter of a cerebral hemisphere, were uncommon. Brain contusion was identified in six (25%). Brain infarction was identified in four subjects (17%).

The outcome of victim of iTBI is severe. Death occurred in four subjects (16.7%). Three of the four fatalities occurred in infants under 12 months old who were suspected to have been shaken. The other fatality occurred in a 3 years old who had epidural haematoma and skull fracture, believed to be impact injury. Residual neurological deficit and morbidity were seen in half of all subjects. Hence only one-third of subjects had a favorable outcome and survived with no neurological abnormality. The clinical outcomes of the 24 patients were summarized in table 1.

Table 1: Outcome of 24 patients with inflicted traumatic brain injury. Unfavorable outcome is defined by death or the presence of neurological morbidity. One patient may have more than one disability.

Normal	8	(33.3%)
Adverse Outcome	16	(66.7%)
Death	4	(16.7%)
Motor Impairment	6	(25%)
Hemiparesis	3	
Ataxia	2	
Quadriparesis	1	
Cognitive Impairment	11	(45.8%)
Mild grade MR	4	
Moderate grade MR	5	
Severe grade MR	2	
Epilepsy	5	(20.8%)

In an attempt to identify the predictive factors for unfavorable outcome, univariate analysis was performed for some of the presenting symptoms, modes of brain insult and clinical findings to the occurrence of unfavorable outcome, defined as death or presence of neurological abnormality afterwards. None of the following factors was found to associate with unfavorable outcome to a significant level: presence of subdural haematoma to any extent, presence of brain infarction or brain contusion, hypotension on admission, the need for artificial ventilation or resuscitation and the presence of seizure on presentation. Only the need for ICU admission, which reflected a generally poor physical condition, was found to associate with poor outcome ($p=0.032$). Hence the sicker the victim, the poorer the outcome.

Discussion

This study showed very similar results to other studies on inflicted traumatic brain injury. The death rate usually quoted is about 15 - 20%, and for the survivors about half will be badly affected. The finding of this study is very much in keeping with the results elsewhere.

Inflicted traumatic brain injury is an important and preventable cause of death and neurological morbidity. Its diagnosis is almost never straightforward. This is particularly true in shaken baby syndrome. The clinical history is often elusive or unreliable, and the circumstances surrounding the onset of symptoms are often nebulous. The severity of the brain insult however is often seen as grossly out of proportion to whatever the witnesses described, and hence the alarm is rang about the possibility of foul play. The difficulty in getting a truthful account of what happened also caused a lot of uncertainties in the research of this enigmatic condition.

Obviously it is impossible to study the effect of shaking in human infants because of ethical reasons. But by animal studies it was demonstrated that the onset of symptoms is almost instantaneous. After shaking the test animal, apnoea, hypotension, seizures and pallor occurred almost instantaneously after the insult. This is supported by a study of 95 infants who died after accidental head injuries.[1] Therefore when an infant sustained brain insult and retinal haemorrahge that are compatible with shaking, but the caregiver denies any lapses of attention and noticed no significant injury, investigation toward the possibility of non-accidental head injury would be justified.

During shaking the displacements in the brain occurred in a heterogeneous manner. Shaking does not only cause a forward-backward acceleration-deceleration translational movement of the brain, which is the movement experienced in trivial falls and result useally in no harm. It also causes angular or rotational movements within the brain parenchyma that lead to shearing injuries to the neurons, tearing the axons from the soma of the nerve cells.[5] If the shaking is compounded by impact (when the head of the infant hits against a hard surface), brain contusion occurs. The contusion results from direct blunt injury to the brain and can lead to injury to the neurons. The extent of neuronal loss from these two modes of insult probably determines the occurrence of neurological morbidity. The presence of subdural haemorrhage, which is a result of the bridging veins being torn by the translational movements of the forward-backward, acceleration-deceleration type, only indicates that significant force had been applied to the baby and the magnitude exceeds those forces that an infant will encounter in normal childcare routines. It is more of a marker to tell what sort of injury had occurred. It however does not determine the outcome, as seen in this study.

Shaking also causes impingement of the cervico-medullary junction against the base of skull. This injury has direct impact on the regulatory centres of blood pressure, breathing and conscious level

situated within the medulla. Thus the occurrence of hypotension, apnoea and impaired consciousness are commonly observed clinical features. These physiologic disturbances would require supportive treatment to avoid secondary injury to the brain.

The impact on the physiology of the whole infant is so diverse in shaking injury that no one factor predicts outcome, as shown in this study. The extent of injury is determined by not only the direct hit on the neuron by force, but also by the secondary insult arising from hypotension and hypoxia.

Over the past five years there have been new hypotheses, supported by animal studies or pathological findings, put forward against the conventional wisdom about shaken baby syndrome. Previously retinal haemorrhage, which is uncommon in normal infants older than 30 days, was thought to be a result of raised venous pressure that arises from the gripping of the thorax that leads to increased pressure in the central retinal vein. Now there is evidence that retinal haemorrhage can arise due to hypoxia alone. Geddes reported in 2001[3,4] that in his series of 37 infants aged nine months or below who died of inflicted head injuries, shearing injury or diffuse axonal injury was found only in two subjects. Diffuse hypoxic damage was the commonest finding. Injury to the brainstem and upper spinal nerve roots was found in eleven subjects. He argued that a stretching injury to the cervico-medullary structures, which involves substantially less force than shaking, can lead to the hypoxic insults. This new hypothesis had created much heated discussion. In fact Geddes was personally involved in a court case in United Kingdom, acting as an expert witness of the defence attorney. Although the court ruled that the diagnosis of shaken baby syndrome was still valid in that case,[6,7] we can expect more and more challenges against the diagnosis of shaken baby syndrome, both at medical and legal fronts.[8] So at the moment inflicted traumatic brain injury is far from a conclusive story. New developments are on the horizon and paediatricians should keep track of any new developments in future. Nonetheless it is always wise to advise parents and caregivers never shake their babies.

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A Young Girl with Biotinidase Deficiency Presented with Guillain-Barre like Syndrome and Later with Ataxia and Alopecia

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Case Summary

A thirty-two months old Chinese girl manifested a history of recurrent bilateral lower limb weakness. She had Klebseilla septicaemia and pneumonia during neonatal period. She was noted to have stridor since 6 months of age and was found to have mild laryngomalacia on conservative management. She had regular follow up in general paediatric clinic and had showed normal developmental milestones. At twenty-months of age, she developed bilateral lower limb weakness 3 days after MMR vaccination and fourth dose of oral polio vaccine. She was bed-bound with truncal hypotonia 10 days after vaccination. She was admitted to the paediatric department of a general hospital, presenting with ascending limb weakness. Physical examination showed bilateral flaccid paralysis of lower limbs with power of grade 3/5 and areflexia while upper limbs had power of grade 4/5 and normal reflexes. She was managed as Guillain-Barre Syndrome with intravenous immunoglobulin at a dosage of 2g/kg. She developed progressive limbs weakness with respiratory involvement. Investigations showed normal complete blood count, normal liver and renal function study, no metabolic acidosis, no hypoglycemia, normal muscle enzymes. Cerebrospinal fluid study showed normal cell counts, biochemistry and negative bacterial culture. Nerve conduction study was compatible with polyradiculopathy. MRI brain and spine showing hyperintense signal from dorsal brainstem down to T2 level and cervial cord was swollen from C2 to C6 level.

She was transferred to Queen Elizabeth Hospital for ventilatory care 7 days after her hospitalization. Ophthalmologist assessment showed no optic neuritis or atrophy. Electroencephalogram revealed diffuse cerebral dysfunction. Repeated lumbar puncture revealed normal cell counts and biochemistry, negative bacterial culture and viral study (including enterovirus, varicella zoster virus, herpex simplex virus) and also negative for oligoclonal band. Paired sera for viral study were negative (including influenza A/B, mycoplasma, enterovirus, measles, mumps). Blood for EBV serology was normal. C3/C4 and ANF were all negative. Repeated MRI brain showed T2-hyperintensities in grey-white matter junctions of both cerebral hemispheres with early brain atrophy while MRI spine revealed abnormal signals involving brainstem and spinal cord with enchancement of doral column of upper cervical cord and periaqueductal area. She also had abnormal BAEP and VEP responses on both side. She continued to run a downhill course. Pulsed methylprednisolone treatment was started 10 days after first admission and was followed with oral steroid therapy. She was able to wean off from ventilator but the progress was very slow afterwards. Plasmapheresis was tried at 19 days after admission. She gradually improved but ended up with spastic paraparesis. She was discharged after 2 months. The diagnosis then was suspected to be vaccination related acute encephalomyelitis.

Subsequently, she had regular follow- up in our neurology clinic with gradual improvement. She started tiptoeing with support and spoke with three-word phrase at 24 months of age. Follow-up MRI brain and spine revealed improvement of abnormal signal over posterior brainstem and upper cervical cord at 25 months of age.

She presented to the emergency department again at 32 months old with poor appetite and malaise that were associated with an episode of acute upper respiratory tract infection. She was very unsteady with marked truncal swaying at standing. She was also unable to walk. She was reported to have alopecia since 30 months of age. Examination revealed an alert child with slow response to question and stimulation. At first she was found to have strands on hair on her pillow and there was no patches of complete alopecia. However after about on week of admission she started to develop periorbital erythematous skin rash, patches of alopecia over occipital and parietal area, slurred speech, truncal ataxia and spasticity over lower limbs with tight tendon Achilles. Both her lower limbs showed a power of grade 3.

Investigations at this admission showed no metabolic acidosis or hypoglycemia. Her electrolytes and ammonia level were normal. Her lactate level was slightly raised at 2.7mmol/L and the pyruvate level was elevated at 192μmol/L. Her urine for organic acid chromatography showed increased amount of 3-hydroxyl propionic, 3-hydroxyl isovaleric and methylcitric acid. This finding was consistent with multiple carboxylase deficiency. Later, serum for biotinidase study showed very low activity (0.3 nmol pABA/min/ml) and was consistent with biotinidase deficiency. She was put on oral biotin 10mg daily. Alopecia and skin rash resolved within 2 months of treatment. Currently she managed to walk with support in more erect posture, but spastic paraparesis still persisted. Her voluntary control of the lower limbs was poor. She received one time of Botulinum toxin A injection into her medial hamstrings and gastrocnemius at 40 months old. Her gait improved after the relief of spasticity. Her vision and hearing were preserved, and her speech development caught up and now she could speak complete sentences and express her intentions verbally.

Discussion

Biotin is a B-complex vitamin that is covalently bound as a cofactor to a number of carboxylases. There are altogether four carboxylases that are affected by a lack of biotin, namely pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase (three mitochondrial enzymes) and acetyl-CoA carboxylase (a cytosolic enzyme). Biotinidase is the enzyme that cleaves biotin from holocarboxylase. Failure of this process due to biotinidase deficiency leads to reduced biotin reformation and impaired carboxylase function.

Biotinidase deficiency, defined as a level of less than 10% of mean normal serum activity, is an autosomal recessive disorder. Age of onset ranges from several months to several years due to the presence of sufficient free biotin derived from the diet. Onset may be either acute or insidious, with steady disease progression, or with acute exacerbations mingled among asymptomatic periods. The most common clinical syndrome consists of dermatologic, neurologic, metabolic and immunologic abnormalities. Dermatologic finding include periorbital cracking lesions, keratoconjunctivitis, corneal ulcers, and hair loss/thin hair. Metabolic derangements include episodic or profound metabolic and hypoglycemia. Patients may present acutely with coma and hypothermia. Impaired T/B cell immunity may lead to severe infection. Common neurologic manifestations include seizure, ataxia, developmental delay, hypotonia, and optic or auditory neurosensory deficits. The prevalence of sensorineural hearing loss is up to 75% in symptomatic patients. Children with delayed clinical onset have optic atrophy, spastic paraparesis and electromyographic evidence of neuropathy as their presenting features. Biochemistry and laboratory abnormalities include lactic acidemia and the presence of lactic acid, 3-hydroxyisovaleric acid, methylcitric acid, 3-methycrotonylglycine, 3-hydroxyproprionic acid and triglyglycine in the urine. Cerebrospinal fluid may showed increased lactate and pyruvate level.

Measurement of biotin of blood and urine will showed diminished levels. It should be noted that the urine organic acid excretion does not differentiate biotinidase deficiency from another rarer but more severe condition, holocarboyxlase synthase deficiency. Diagnosis of biotinidase deficiency is made by serum biotinidase assay.

Serum biotinidase activity assay is used as a screening test for all newborns in certain countries. However as the prevalence of biotinidase deficiency is low in the local population, it is not included in the universal newborn screening program in Hong Kong.

The gene of biotinidase is localized to chromosome 3p25. There are more than 60 different mutations reported thus far. All these mutations were reported in non-Chinese populations.

Our patient's findings suggest that she manifested an intermediate form of clinical presentation. The onset was at the end of second years of life with acute onset of ascending weakness and hypotonia in the presence of marginal biotin deficiency caused by stress like vaccination. It is the occurrence of symptoms after vaccination that has contributed to the initial diagnosis of vaccine-related encephalomyelitis. She developed spastic paraparesis accompanied by the presence of myelopathy on spinal MRI, a finding described in children with onset after 5 years of age. Then she had a relatively asymptomatic period with slow recovery, followed by a typical presentation with hypotonia, ataxia, skin rash and alopecia. However, she was atypical in that she did not have significant metabolic derangements and history of repeated sepsis. Involvement of spinal cord should be considered a feature of biotinidase deficiency, irrespective of the age of presentation as our patient had spastic paraparesis early in the presentation. The presence of desquamating skin rash, periorbital rash and alopecia together with neurological symptoms of various sorts should prompt the test for organic acid chromatography. If the test is not immediately available, a large of biotin supplement can be given safely so as not to delay the possible benefit from treatment, as although the skin condition and metabolic disturbance can be completely restored, the neurological insults are not always reversible.

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An Infant with Intractable Seizures, Peculiar Facial Features and Retinal Abnormalities

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Case Summary

This Nepali girl was born at 40 weeks gestation to non-consanguineous parents. She was referred to the Obstetric Department of Queen Elizabeth Hospital of breech presentation at term. Antenatal ultrasound examination identified the presence of hydrocephalus and absence of corpus callosum. Emergency caesarean delivery was performed. She was born weighing 3.56 kg and no resuscitation was required. Her head measured 37 cm at birth, which was above the 97th centile for newborns.

After birth she was found to have an unusual facies. Her face was flat and the nasal bridge was depressed. The antero-posterior diameter of the head was decreased. There was increased hair growth over the forehead, forming an unusually low anterior hairline. Her palpebral fissures were narrow and down-slanting. Her mouth was small and triangular (figure 1). There was no coloboma seen in the iris. She had congenital developmental dysplasia of the left hip with dislocation. Her vision was poor and no visual fixation was seen. She failed the brainstem evoked potential screening and formal audiometric assessment could not be done. She was also detected to have elevated TSH levels and congenital hypothyroidism was diagnosed.

Owing the detection of hydrocephalus and a large head, a CT brain was performed. It confirmed the presence of colpocephaly, agenesis of corpus callosum. There was no evidence of Dandy-Walker malformation or Arnold-Chiari malformation on the scan. MR brain later also confirmed similar finding (figures 2 & 3).

Her head size had remained static and there was no evidence of raised intracranial pressure. Hence the hydrocephalus was managed conservatively without shunting at first.

She had a normal karyotype of 46 XX. Viral study did not identify any congenital infection.

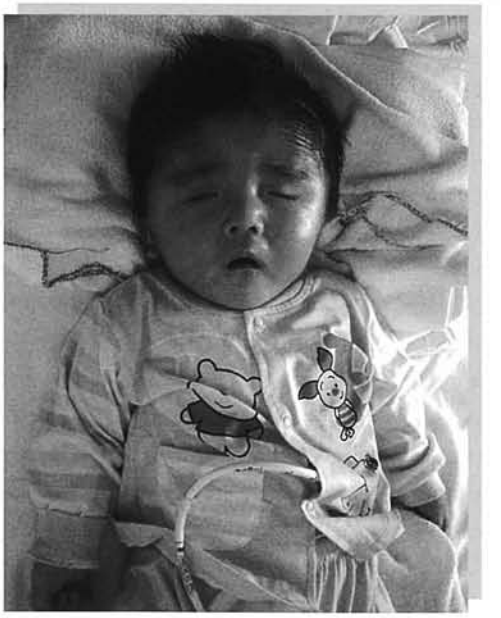

Figure 1: Somatic features and facies of the patient. Notice the broad and flat face, hirsute forehead, downslanting eyes, small mouth and a relatively hypoplastic right fifth finger.

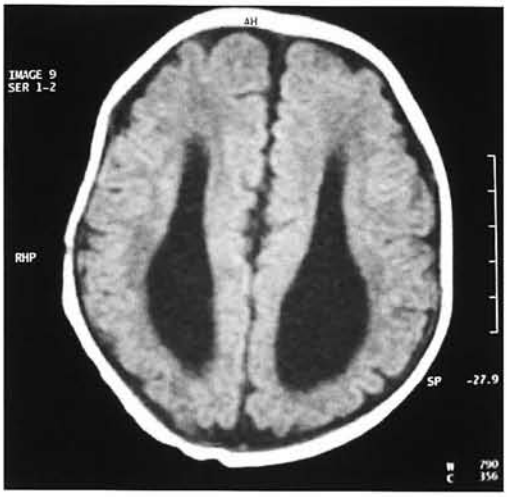

Figure 2: CT Brain showing colpocephaly. The posterior horns of the lateral ventricles are dilated and the bodies were parallel to each other without meeting the third ventricle.

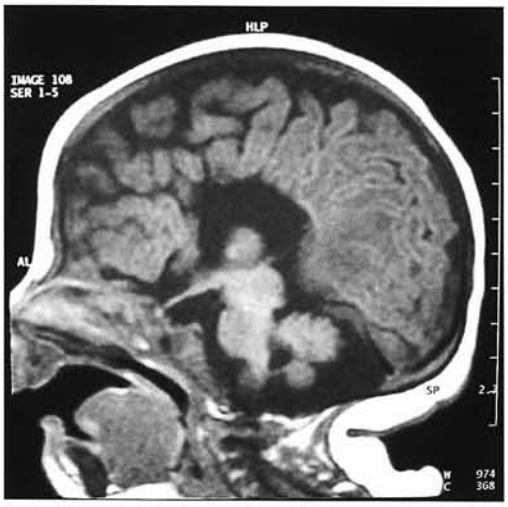

Figure 3: Sagittal MR view showing the absence of corpus callosum and the dilated posterior horn of the lateral ventricle. The gyral pattern over the parietal region appears indistinct and abnormal. The cerebellum and the posterior fossa also appear small.

She later suffered from one episode of chest infection in the first month of life. Chest X-ray taken showed fused dysplastic ribs. She was also found to have a secundum atrial septal defect and peripheral pulmonary stenosis. She did not develop heart failure despite the heart disease.

At one month old she started to develop occasional flexor spasms affecting mostly the upper limbs. Her head would turn to the right side during the seizure. These seizures were quite violent and sometimes were associated with vomiting. She appeared very tired after these seizures. The frequency of seizure gradually built up to once every two hours when she was five months old. Electroencephalography showed modified hypsarrhythmia but her seizures were not typical of infantile spasms. They are more akin to complex partial seizures. She was hence put on sodium valproate and then phenytoin and carbamazepine, all to no avail. She was later changed to the combination of sodium valproate and lamotrigine when she was 7 months old and benefit was seen.

Neurosurgeon decided to put in a ventriculo-peritoneal shunt for her hydrocephalus when she was showing arrest in development and frequent seizures at 5 months old.

Ophthalmologic assessment for her poor visual acuity found retinal lacunae in her eyes. A coloboma was suspected at first but was not later confirmed.

Her oromotor dysfunction was severe. She had repeated choking which had been difficult to prevent. Percutaneous endoscopic gastrostomy was performed and she was fed exclusively through the gastrostomy since 9 months old.

Synthesizing all these clinical features, this little girl was diagnosed to have Aicardi syndrome. The key characteristics are:

(1) Female gender
(2) Agenesis of corpus callosum
(3) Retinal lacunae and
(4) Intractable epilepsy

She had been managed on ambulatory basis. Infrequent hospitalization was required. Her seizures were only fairly controlled with a high dose of sodium valproate of up to 60 mg/kg/day and lamotrigine at 7mg/kg/day. Fortunately chest infections are not common. At the time of press she is 26 months old. There had been little cognitive progress and she remained totally dependent on care and bed-bound.

Discussion

Aicardi syndrome is a rare X-linked dominant condition. Its gene loci is believed to lie on Xp22.3. All cases are not familial. The condition is invariably linked with poor neurological prognosis with shortened longevity. There are however occasional reports of affected girls with only moderately or mildly impaired cognitive functions. And a recent report also told of a patient who had no seizures.

Agenesis of corpus callosum is a major feature of the syndrome. The characteristic radiological finding is colpocephaly, where the two lateral ventricles appear to run parallel to each other. This is because of the lack of crisscrossing fibers across the corpus callosum forces all the long tracts to run alongside the lateral walls of the two lateral ventricles, thus changing the walls of the lateral ventricles to a straight contour running parallel to each other.

Retinal lacunae are irregularly distributed "holes" in the choroid and retina. They are different from colobomas, which are sectorial deficiency in the development of the globe. Colobomas are often seen in addition to lacunae in Aicardi syndrome.

Regarding the external somatic features of Aicardi syndrome, a recent report of 40 cases from United States reported prominent pre-maxilla, upturned nasal tip and sparse eyebrows, micro-ophthalmia and skin nevi or vascular malformations (haemangioma) are present in a significant proportion of subjects. There are also hand abnormality such as camptodactyly, proximally placed thumbs and hypoplasia of the fifth finger.[2] These features might be useful hints to the underlying diagnosis of Aicardi syndrome.

Although infantile spasms is part of the classical triad (callosal agenesis, chorioretinal lacunae and infantile spasms) in Aicardi syndrome, focal seizures are more commonly encountered.[2] Treatment with anti-epileptic drugs is met with poor response in most patients.

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All that Twitches is Not Tics (or Epilepsy)

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Case Summary

The boy, who is now 11 years old, presented with involuntary "spasms" of his limbs when he was seven years old. He had an inflammatory fibrosarcoma of his left kidney when he was seven months old. It presented as a palpable abdominal mass. The massive tumour and the left kidney were removed surgically when he was eight months old. The tumour was deemed to be of low malignant potential. No adjuvant chemotherapy or radiotherapy was given. He had remained free of relapse throughout the past years.

He remained healthy despite the surgery. He was hyperactive and had fair school performance ever since he started kindergarten. No medication was required for his hyperactivity.

When he presented with the involuntary spasms he described that his four limbs were rigid and frozen. He did not lose consciousness. Sometimes there was facial grimacing also. His hands would be fisted. He was unable to suppress these movements by will. Each attack last for a few seconds only. After the attacks he seemed to have great difficulty in moving again. He did not have autonomic signs of sweating, shortness of breath or palpitation. He indicated that these attacks were precipitated by stress and running.

Examination essentially showed no abnormality. No such spasm was ever witnessed by clinicians.

Having epilepsy as the working diagnosis, an electroencephalogram was done. The report later returned to be normal. CT brain also showed no abnormality. Blood and urine tests were normal. Anti-streptolysin O titre was normal.

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As there was no evidence of epilepsy, he was referred to the child psychiatrist for assessment. The possibility of tics or behavioral problem was considered. Pimozide, a treatment commonly used for tics, was tried but apparently it only led to partial improvement and had caused significant sedative side effects.

Upon reviewing the family history it was revealed that the mother, her brother and her nephew and nieces also had similar problem. They were however dismissed or disregarded. Mother later recounted that she when she tried to lift weight with one arm the other arm would sometimes hyperextend in an awkward manner. The limbs spasms of the patient were also provoked by initiation of movements.

After reviewing the history the diagnosis of paroxysmal kinesiogenic dyskinesia of the dystonic type was made. He was put on a small dose of carbamazepine 5mg/kg/day. His response was complete and there had not been any attack while he was on the drug. He did not experience any side effect.

Discussion

Paroxysmal dyskinesias are a group of disorders that are commonly misdiagnosed. There are four major types, described by their associated triggers. They are:

(1) Paroxysmal kinesiogenic dyskinesias (PKD) – precipitated by initiation of movements or sudden unexpected stimuli or startle.
(2) Paroxysmal non-kinesiogenic dyskinesia (PNKD) – not precipitated by initiation of movements.
(3) Paroxysmal exertion-related dyskinesia (PED) – precipitated by prolonged exertion and
(4) Paroxysmal hypnogenic dyskinesia (PHD) – movement associated with non-REM sleep.

Paroxysmal dyskinesias can also be classified as idiopathic or symptomatic. The idiopathic group is often familial. For idiopathic PKD it is postulated to be related to an abnormality of the voltage-gated sodium channel. The gene for idiopathic PKD is mapped to chromosome 16. While symptomatic PKD is usually associated with hypothyroidism, anoxic insult or calcification of the basal ganglia, cryptogenic myelitis or other brain malformations.

PKD is not an uncommon condition in the local population basing on the author's personal experience. There are four types: choreic, athetotic, ballistic and dystonic. The patient reported here is compatible with the dystonic type.

PKD is likely to have been under-recognized. It has no diagnostic test. Diagnosis relies on clinical history. A family history would be very helpful, and the classical description of awkward spasms and postures of the limbs that are associated with movements or sudden stimuli should be obtained. It differs from tics in that the spasms or twitches cannot be voluntarily suppressed at all, while in tics usually some degree of voluntary suppression is possible. A typical spell of PKD usually last for seconds to minutes. Any of the four limbs can be affected and in any combination. The limb is usually retracted or hyperextended. One patient whom the author sees had attacks in the manner that the shoulder is adducted and internally rotated, elbow flexed and held in front of the chest, the wrist would be flexed and the fingers extended at the interphalangeal joints while flexed at the metacarpo-phalangeal joints, forming what is known as the "obstetrician's hand" seen in carpopedal spasms. Of course other awkward postures are possible. Frequency of seizure can vary from one attack in several days to more than 100 a day. This condition tends to improve with age, and some patients may enjoy long period of remission.

The differential diagnoses of PKD include epilepsy, tics, carpopedal spasm, hyperekplexia and psychogenic disorders. EEG and brain imaging are indicated in most cases to exclude underlying condition and exclude epileptic seizures.

As a channelopathy, PKD is expectedly amenable to drugs that modulate ion channels. Anti-epileptic drugs, including phenytoin, sodium valproate, phenobarbitone, pimidone, acetazolamide and benzodiazepines are helpful in controlling symptoms. In the local population it appears that carbamazepine is a very effective option. A low dose often suffices in PKD.

The other paroxysmal dyskinesias are much rarer than PKD. Table 1 summarizes these conditions.

Paroxysmal abnormal movements are common complaints in children. While a lot of them are tics or epileptic in origin, other diagnostic possibilities has to be considered. Once the diagnosis is made and treatment given appropriately the result is often gratifying.

Table 1: Different paroxysmal dyskinesia, their gene loci and reported treatment options

Disease	Gene Loci	Treatment
Paroxysmal kinesiogenic dyskinesia (PKD)	16p11.2 - q12.1	Carbamazepine Sodium Valproate Phenytoin Benzodiazepines e.g. clonazepam Phenobaribitone Primidone Acetazolamide ?L-dopa
Paroxysmal non-kinesiogenic dyskinesia (PNKD)	2q33-35	Clonazepam Anti-epileptic drugs are less effective Trihexyphenidyl Haloperidol
Paroxysmal exertion-related dyskinesia (PED)	16p11.2-q12	Clonazepam Carbamazepine
Paroxysmal hypnogenic dyskinesia	20q13.2-13.3	Carbamazepine Phenytoin ?Acetazolamide

Journal Review

Buccal Midazolam in Acute Treatment of Childhood Seizures

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The Study

This randomized controlled trial conducted in four hospitals emergency rooms in the Midlands region of the United Kingdom studied 177 patients with 219 separate attendances (or patient-episodes) with ongoing seizure. The age of the patients is from 6 months to 15 years, median age being 3 years old. By randomization 110 patient-episodes received rectal diazepam 0.5mg/kg and 109 patient-episodes received buccal midazolam 0.5 mg/kg. The intravenous preparation of midazolam hydrochloride was administered by a straw or needle between the gum and the cheeks. Success of treatment is defined by cessation of seizure within 10 minutes of administration of drugs. This study did not discriminate patients with the first seizures or those who had chronic epilepsy. All except five episodes of partial seizures were generalized tonic-clonic seizures in this study. Seventy-two percent of the total patient-episodes were known to have precious seizures and 53% were receiving anti-epileptic drugs (AED) at study time. In 31% of patient-episodes pre-hospital emergency treatment with rectal diazepam or paraldehyde was given.

The baseline characteristics of the two populations were similar. However the group that received buccal midazolam showed superior result in terms of higher rate of successful cessation of seizure within 10 minutes of drug withdrawal, shorter time to seizure cessation and fewer seizure recurrences after cessation. Buccal midazolam was associated with similar number of episodes of respiratory depression as rectal diazepam; about five percent of both groups experienced this side effect, some were so severe that intubation and transferal to intensive care was necessary.

Discussion

The property of midazolam having both water-soluble and lipid-soluble characteristics makes it a unique drug that can be administered through mucosal surfaces and also allow rapid penetration into the central nervous system. Hence its use in emergency treatment for stopping seizures had been exploited for many years. Intranasal route and now buccal route have been studies and in general the results are favorable. The mucosal route allows quick administration without having to wait for the setting of vascular access. It also avoids the embarrassment of having to undress a child in the rectal administration of diazepam. However the preparation of midazolam currently available is a major hurdle. Midazolam hydrochloride solution comes in ampoules or vials and would require the use of syringe for accurate dosing. So before the development of a more convenient mode of drug delivery, the use of transmucosal midazolam will remain restricted to ambulance, emergency rooms, clinics and hospitals. It would be difficult for parents to make use of this mode of emergency treatment at home.

The treatment of prolonged seizures requires decisive and prompt intervention. It is generally believed that the sooner treatment is administered, the better the response would be. Buccal midazolam is amongst once of the easiest methods of giving benzodiazepines to children, especially when they are in recovery position. It also averts the foreign body sensation association with intranasal administration.

The dosage for buccal midazolam still requires some fine-tuning. The dosage used in this study is higher than most other studies, i.e. 0.2-0.3mg/kg. Considering the 5% chance of respiratory suppression at the higher dose of 0.5mg.kg, we should aim at finding a safe dose with reasonable efficacy in aborting seizures. Before any such definitive guidelines exist, discretion of the clinician should be exercised if he chooses to use buccal midazolam.

As a general rule a convulsing child who received benzodiazepines by whichever route should be prepared for artificial ventilation. We should probably consider educating parents more readily about how to support ventilation for their children, instead of having them to improvise at an unnerving frenzy when their children stop breathing after receiving benzodiazepines. As clinicians we should also be ready to ventilate a child having seizure, whether for just a brief moment by mask bagging or for hours by endotracheal intubation and ventilator.

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Journal Review

α-[^{11}C] Methyl-L-Tryptophan Positron Emission Tomography for Epileptogenic Tuber Identification in Tuberous Sclerosis

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The Study

This study, performed at Children's Hospital of Michigan, tried to assess the value of using a special PET together with a number of other tools in evaluating children with tuberous sclerosis (TS) for epilepsy surgery. They have demonstrated in other preliminary studies that PET utilizing α-[^{11}C] Methyl-L-Tryptophan (AMT), a tracer of serotinon synthesis and tryptophan metabolism via the kynurenine pathway, is able to identify epileptogenic tubers as defined by seizure pattern and ictal EEG in about two-thirds of TS patients with intractable epilepsy. They therefore put this modality of localization to the ultimate test: studying the outcome of these patients when their surgery was planned with the use of this PET.

Out of the 87 children who had AMT PET at the PET Centre of the Children's Hospital of Michigan, 17 underwent epilepsy surgery at the same hospital. Their age ranged from 4 months to 12.3 years, the mean age at surgery being 4.7 years. Three subjects received one-stage surgery with intra-operative electrocorticography (ECoG) to define the extent of resection. The remaining fourteen underwent at two-stage operation, first by implantation of subdural grid electrodes for monitoring and at the second stage the definitive focal cortical resection or lobectomy was done. Two out of these 14 patients required a second operation.

In the study apart the conventional video EEG, MRI and Flurodexoyglucose (FDG) PET these subjects also received AMT PET at 0.1 mCi/kg. Tubers in TS are nodular lesions in the cerebral cortex with hyperintensity at FLAIR or T2 weight sequence, sometimes with calcification, and also hypometabolic on FDG PET. FDG PET however does not differentiate tubers that are epileptogenic from those that are not. AMT PET will light up epileptogenic tubers by showing increased tracer uptake by more than 5% compared with the surrounding cortex.

There were altogether 179 tubers identified in the 17 subjects who eventually underwent surgery. Out of the 179 tubers, 30 tubers were hot of AMT PET in 16 patients, and they do not always agree with the scalp EEG localization. In one patient the AMT PET pinpointed an area adjacent to a large tuber. For this particular patient the tuber with the adjacent cortex was removed and resulted in seizure freedom.

The outcome of surgery having utilized AMT PET in these 17 patients was remarkably good in 12 patients who achieved freedom from seizure. Two patients obtained worthwhile improvement, and three had no improvement.

It should also be noticed that in one patient whose seizures did not benefit from the surgery done at 1.7 years old, the authors reported considerable cognitive improvement, although the cognitive evaluation data are not available in the report.

Discussion

Tuberous sclerosis is a notorious situation associated with intractable epilepsy. Epilepsy surgery is an obvious choice but the outcome is often unpredictable. This is believed to be the result of the widespread cortical malformation and the difficulty of localizing the epileptogenic area. This study has demonstrated a method of localizing the epileptogenic tuber which produced rather polarized results. While the majority of the study population benefited, a sizeable proportion failed to derive any benefit. This finding probably indicates that while AMT PET is useful in providing better localization confidence is some patients and its role is still ancillary at best. Its value is probably highest in those patients who have multiple tubers. Concordance with other localization techniques like EEG, ECoG and invasive subdural monitoring, is still paramount.

It should be pointed out that the extent of the surgery performed in this study is about the same as other studies not utilizing this PET. Extensive surgery is often required for tuberous sclerosis, probably not because of the inability to pinpoint the epileptogenic zones in TS, but the epileptogenic zones of TS are necessarily extensive.

This article contains a lot of detailed specification of the PET scan parameters and can be a useful reference for those who wish to repeat the investigation or utilize it in their clinical practice.

This study rekindles the hope of offering epilepsy surgery for some previously unfavorable candidates. More information about this tool is eagerly awaited.

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Society News

Upcoming Meeting

Annual Scientific Meeting (11 - 14 November 2005)

We are proud to announce our Annual Scientific Meeting of the year 2005, which will take place on 11 - 14 November with the theme on "Neuromuscular Disorders of Infancy, Childhood and Adolescence". Our Course Director will be the world famous Dr H. Royden Jones, Jr., MD., Clinical Professor of Neurology, Harvard Medical School, Director of Electromyography Laboratory, Children's Hospital Boston, Chairman of Division of Medical Specialties, Lahey Clinic, Massachusetts. He will address us on important topics and the most up to date development in the field of paediatric neuromuscular disorders. The meeting provides a great opportunity for local professionals to learn from the world famous expert and at the same time serve as a platform for sharing of experience and knowledge in the fields of Child Neurology and Developmental Paediatrics.

The highlights of this meeting will be a Case Discussion Forum on Saturday 12 November 2005 and also a plenary lecture on 14 November 2005 (Monday) evening on "Paediatric Neurology From the Perspective of Adult Neurology" at the Hong Kong Marco Polo Hotel.

The Annual Scientific Meeting starts on 11 November 2005 with an evening lecture and continues throughout the weekend and ends on Monday evening. There will be different local presentations, free paper presentations and also plenty of time for meeting your colleagues. Please do not miss this opportunity.

Registration can be made with Ms. Karen Po at 22/F., Oxford House, 979 King's Road, Taikoo Place, Island East, Hong Kong or by Fax at 2599-8990 and Tel.: 2599-8851.

Neurology Conference (14 December 2005)

The next Neurology Conference will be held on 14 December 2005 at Kwong Wah Hospital. If you wish to present interesting cases for discussion, please contact: Dr Sam Yeung or Dr Ada Yung at hkcndp@hongkong.com

Meeting Announcement

International Symposium on "Status Epilepticus in Infants and Young Children: Basic Mechanisms, Clinical Evaluation, Treatment and Prognosis"

The symposium will present an overview of current knowledge on status epilepticus, concerning basic mechanisms, clinical evaluation, treatment and prognosis. The delegates are invited to participate in this special symposium and to visit historical sites of Osaka and Kyoto, Japan.

Date	:	29-30 April 2006
Venue	:	Senri Hankyu Hotel, Osaka Japan
Organized by	:	Infantile Seizure Society, Japan
President	:	Toshisaburo Nagai, MD, PhD.
Deadline of Abstract submission	:	31 January 2006 Early registration before 31 January 2006.

For information and registration please contact:

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