Indian J Pediatr
DOI 10.1007/s12098-013-1330-2

CLINICAL PEARLS

Clinical Pearls in Pediatric Neurology

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Received: 17 August 2013 / Accepted: 26 December 2013

Abstract The authors present three neurological cases (common and uncommon), that have important management implications. The specific diagnosis can be suspected clinically if the clinician is aware of the entities. Besides clinical clues, the recognition of important findings in MRI brain is highlighted. The first case is a child with developmental delay, the second case is a child with acute encephalitis like presentation, the third is a child with deteriorating school performance and the fourth is a child with raised intracranial pressure. The authors also present concise review of the topics.

Keywords Acute encephalitis · Biotinidase deficiency · Developmental delay · Glutaric aciduria I · Raised intracranial pressure

Case 1: A Child with Developmental Delay

A 7-mo-old boy was brought with complaints of delayed milestones and rash over the face, spreading over to neck and cubital fossa, noticed for last 2 mo. He was born of second degree consanguineous marriage to a third gravida mother (previous one abortion and one normal live issue) by normal vaginal delivery. He had not attained neck holding and had only recently attained social smile. There was decreased auditory attentiveness in response to sounds. He never had seizures. On examination, occipitofrontal circumference (OFC) was 42 cm (normal range). He had fading skin rash and sparse hair over head. Forehead was prominent. Fundus was normal. He had mild hypotonia with brisk deep tendon reflexes (DTRs).

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Published online: 16 February 2014

Questions

1) What is your clinical differential diagnosis on the basis of history?
   a) Biotinidase deficiency
   b) Multiple carboxylase deficiency
   c) Intrauterine infection
   d) Hypothyroidism

The clinical possibility was neurometabolic disorder (biotinidase deficiency, multiple carboxylase deficiency), in view of consanguineous marriage, skin rash and decreased auditory attentiveness.

2) How will you confirm the diagnosis in this child?
   a) MRI brain
   b) Tandem mass spectroscopy
   c) Arterial blood gas
   d) Enzyme assay

MRI brain showed mild frontoparietal cortical atrophy. Thyroid function tests were normal. Arterial blood gas analysis and fasting blood ammonia were normal. Tandem mass spectroscopy showed mild increase in valine; which was a non-specific finding. Serum biotinidase activity was low-2 nmol/min/mL (normal >5 nmol/min/mL).

Child was started on 10 mg/d biotin. Parents noticed marked improvement after starting biotin therapy. Over one year follow-up, child was developmentally normal. There was no recurrence of skin rash. Mild alopecia was still persisting.

Discussion

Biotinidase deficiency is a neurometabolic disorder with autosomal recessive inheritance in which the enzyme,

biotinidase, is defective and the vitamin, biotin, is not recycled. Age of symptom onset and severity largely depends upon severity of the enzyme defect. Profound biotinidase deficiency is considered when enzyme activity is 10 % or less and mild deficiency when enzyme activity is 10–30 %. Symptoms usually begin in early infancy. Symptoms include unexplained developmental delay, hypotonia, lethargy, spasticity, ataxia, hearing loss and visual impairment. Dermatologic manifestations are common and include alopecia, eczematous rash (Fig. 1) and mucocutaneous candidiasis [1].

Investigations may show metabolic acidosis, ketosis and lactic acidosis, hypoglycemia and hyperammonemia. The diagnosis can be confirmed by enzymatic testing. Biotinidase deficiency can be detected in affected infants by newborn screening. Molecular genetic testing for mutations in the biotinidase (BTD) gene can be done [1].

Biotinidase deficiency necessitates life-long biotin supplementation. The symptoms are treatable and preventable by administering pharmacological doses of biotin of 5–20 mg/d. It is important to avoid raw eggs in diet as these contain avidin that binds biotin. The prognosis is excellent, however sometimes mild development delay or neurological deficits may persist.

Clinical Pearl

In the presence of any of the following without obvious cause: developmental delay, seizures, hypotonia, hearing/vision impairment, eczematous skin rash, alopecia, and ataxia, biotinidase deficiency must be suspected.

Fig. 1 Child with biotinidase deficiency showing eczematous rash on the face

Case 2: A Child with Acute Encephalopathy

A 15-mo-old previously normal girl presented with fever for 7 d and altered sensorium for 5 d. Her illness began with fever and cough of 2 d. On the third day she had acute onset, rapidly progressive altered sensorium. She was not interacting with the parents and had inconsolable cry. Gradually she became progressively lethargic and stopped feeding. She was the second child born to consanguineous parents. Her perinatal period had been uneventful and birth weight was normal. Her elder sibling had died after an acute febrile illness at the age of 17 mo. On examination, vitals were normal, Glasgow Coma Scale score was 9, head circumference 49 cm (>2SD), length and weight were normal. She had marked generalized rigidity and dystonic posturing. There were no meningeal signs. The cranial nerves were normal; fundus showed bilateral retinal hemorrhages. She was started on antibiotics and intravenous fluids. By second day of hospitalization her sensorium improved. However, she had frequent and severe posturing of her limbs. She also had intermittent opisthotonic posturing. Her fever had subsided on the second day of hospitalization.

Questions

1) What are differential diagnoses in this child?
   a) Acute encephalitis
   b) Acute meningitis
   c) Brain abscess
   d) Neuro-metabolic disorder

2) What investigation/s will help you to narrow your differential diagnosis in this child?
   a) Blood culture
   b) CSF analysis
   c) MRI brain
   d) ABG, Urine ketones, Lactate, Ammonia

The first possibility at this stage was acute viral encephalitis (particularly Japanese encephalitis). In view of consanguinity and previous sib death, a possibility of neurometabolic disorder was also kept. Blood counts and coagulation parameters were normal. Blood gases revealed high anion gap metabolic acidosis and urine ketones were positive. The blood sugar reports were however normal. CSF had normal cytology, biochemistry and negative bacterial cultures; HSV PCR was negative. Her CT head was reported as normal with incidental bilateral temporal arachnoid cysts. MRI brain revealed fronto-temporal atrophy, with T2, FLAIR hyperintensities in the bilateral caudate and putamen (Figs. 2 and 3). The rest of the deep grey matter structures and brain stem were normal.

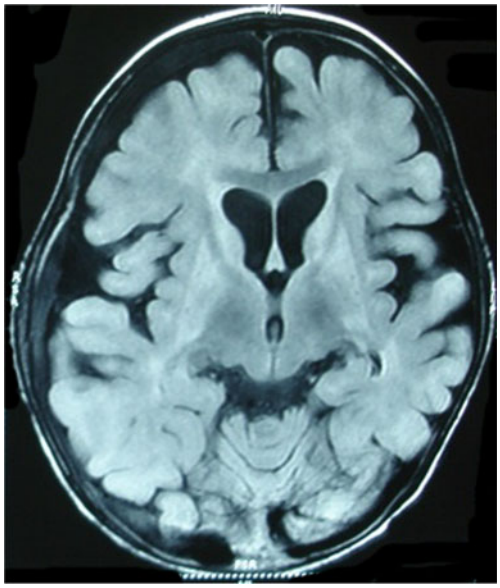

Fig. 2 Axial FLAIR MR image at the level of basal ganglia showing fronto temporal predominant brain atrophy and hyperintense signal changes in bilateral caudate and putamen. Note the mild caudate atrophy

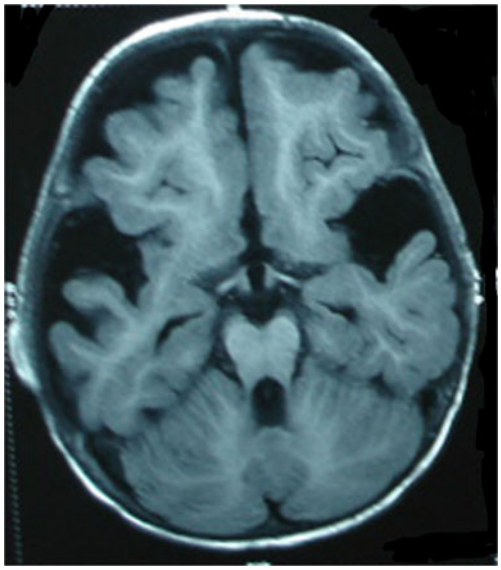

Fig. 3 Axial T1 MR image showing prominent brain atrophy. Note the bilateral temporal cysts

Questions

1) What is the significance of the MRI findings?
   a) Suggestive of encephalitis
   b) Suggestive of neurometabolic disorder
   c) Suggestive of meningitis
   d) Normal variant

2) What investigation/s will help confirm your diagnosis in this child?
   a) Repeat CSF analysis
   b) Blood counts
   c) Tests to detect abnormal urine/blood metabolites

The MRI is suggestive of Glutaric aciduria type I. The diagnosis was confirmed by urine organic acids analysis; it revealed elevated levels of glutaric acid and 3-hydroxyglutaric acid that are indicative of the diagnosis of Glutaric aciduria type I. The patient was started on a low protein diet, riboflavin and carnitine. Prenatal diagnosis was offered to the family.

Discussion

Glutaric aciduria I (MIM-ID*608801) is an autosomal recessive metabolic disorder characterized by progressive extrapyramidal symptoms that usually begin during the first year of life [2]. It results from the deficiency of Glutaryl-CoA dehydrogenase, an acyl dehydrogenase involved in the metabolism of lysine, hydroxylysine, and tryptophan [3]. The clinical profile is variable ranging from acute infantile encephalopathy and sudden death to static dyskinetic cerebral palsy like manifestation. It can also present as progressive dyskinetic syndrome. The affected children have relatively well-preserved intellectual functions and can have macrocephaly. The onset of the extrapyramidal dysfunction can be insidious or abrupt after an infection. Patients can have episodic crises of ketoacidosis, hypoglycemia, hyperammonemia, and elevated serum transaminases. Neuroimaging reveals bilateral atrophy or necrosis of caudate and putamen. Diffuse brain atrophy, particularly fronto-temporal atrophy is very often seen. Diagnosis is confirmed by urine organic acid assay. Recommendations for management include a lysine-restricted diet, supplementation of carnitine and riboflavin [4].

Clinical Pearl

An acute encephalitic presentation in a child with a positive family history and a large head should raise a possibility of glutaric aciduria-I. Typical MRI findings and urine organic acid analysis help to confirm the diagnosis.

Case 3: A Child with Deterioration in School Performance

A 10-y-old previously normal girl presented with worsening in hand writing and deterioration in school performance for last 3 mo. Parents noticed abnormal twisting posture of hands. Onset was insidious and gradually progressive in nature. She also had excessive shyness. There was history of jaundice at the age of 6 y. She was born of non-consanguineous marriage and had two younger sibs. There was no family history of jaundice in the family.

Questions

1) What is your clinical diagnosis on the basis of history?
   a) Wilson's disease
   b) Pantothenate kinase-associated neurodegeneration
   c) DOPA responsive dystonia
   d) Sydenham's chorea

2) Which pathognomonic finding would you like to look for on examination?

The clinical diagnosis on the basis of history was Wilson disease. Other rare causes of secondary dystonia including Pantothenate kinase-associated neurodegeneration and DOPA responsive dystonia were considered less likely.

On general examination, child had mild pallor and Kayser-Fleischer (KF) rings. She did not have icterus. On neurological examination, she had dystonia in upper limbs which worsened on movement. On abdominal examination, liver was not palpable (liver span was 6 cm), and spleen tip was palpable.

Questions

1) How will you confirm the diagnosis in this child?
   a) MRI brain
   b) High levels of serum ceruloplasmin and elevated urine copper excretion
   c) Low levels of serum ceruloplasmin and elevated urine copper excretion
   d) Mutation testing

2) What are the characteristic MRI findings?

The clinical diagnosis of Wilson disease was confirmed by low levels of serum ceruloplasmin and elevated urine copper excretion. MRI of brain revealed characteristic involvement of bilateral caudate and putamen (Fig. 4). Both younger sibs were also screened and were found to have elevated urine copper excretion and low ceruloplasmin levels. They were diagnosed as presymptomatic Wilson disease.

Discussion

In view of slowly progressive dystonia with behavioral changes and deteriorating school performance, neurological Wilson disease is a strong possibility, and one needs to look for Kayser-Fleischer (KF) ring, which is pathognomonic. KF ring represents deposition of copper in Descemet's membrane of the cornea. A slit-lamp examination may be required to identify KF ring in early stages. It

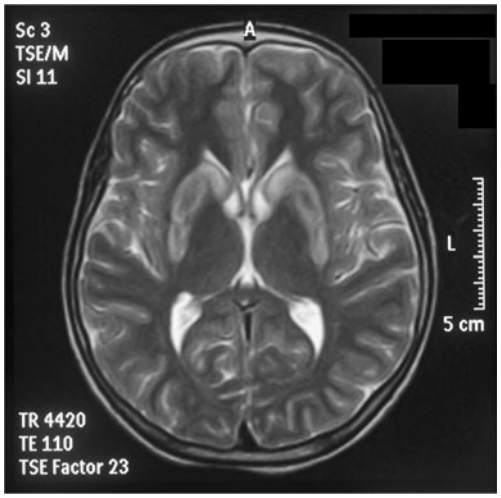

Fig. 4 Axial T2 MR image showing bilateral caudate and putamen hyperintensity

is important to remember that absence of Kayser-Fleischer ring does not exclude the diagnosis of Wilson disease [5]. MRI brain in neurologic Wilson disease may have characteristic bilateral symmetric high signal intensity in the putamen on T2-weighted images. Other peculiar abnormalities including "face of the giant panda sign" and "face of the miniature panda" are occasionally noticed [6].

Clinical Pearl

In a child with progressive dystonia, one should always look for KF ring that indicate Wilson disease particularly because it is treatable. Copper studies help in confirming the diagnosis and in monitoring the treatment.

Case 4: A Child with Raised Intracranial Pressure

A previously well, 4-y-old girl presented with two episodes of seizures in the last 7 d and fever for 1 d. The second episode 2 d prior to the presentation was followed by altered sensorium. On initial assessment the child was seizing and was categorized as "unstable, life threatening" using Pediatric Assessment Triangle (PAT). Her heart rate was 89/min, respiratory rate-28/min, blood pressure-120/80 mmHg, temperature-37 °C and SpO_2 (room air) 99 %. Her glasgow coma scale (GCS) was 9 (E2M5V2), pupils were asymmetric (right 4 mm, left 2 mm) and non reactive. Fundus showed papilledema. There was no cranial nerve palsy, tone was increased in all limbs, decorticate posturing was observed on stimulation, tendon stretch reflexes were brisk, plantars were extensor. Abdomen, respiratory and cardiovascular system examination did not reveal any abnormal finding.

What are the Life-threatening Problems?

1. Fever and possible meningitis
2. Status epilepticus and raised intracranial pressure with herniation

The immediate life threatening problems are ongoing seizures and raised intracranial pressure (ICP) characterized by papilledema, extensor posturing and asymmetric non reacting pupils. While fever and possible meningitis or encephalitis also need management, but they are not of urgent concern.

What is the Immediate Life Saving Measure?

1. Antibiotics
2. Fluid bolus
3. Control of status epilepticus
4. Reversal of herniation and maintenance of the cerebral perfusion pressure (CPP)

Seizures were aborted with intravenous diazepam 0.3 mg/kg followed by phenytoin at a loading dose of 20 mg/kg and maintenance 5 mg/kg/d. Simultaneously, airway was secured by rapid sequence intubation (RSI) and mild hyperventilation was given with bag and tube manually with double the respiratory rate of her age. Dextrose -normal saline (DNS) was started as maintenance fluid. Mannitol (20 %) 0.25 g/kg/dose -2 doses followed by 3 % hypertonic saline 5 mL/kg loading followed by 0.1 mL/kg/h was started, but no response was noted. A contrast CT head revealed right hemispheric hypodensity with uncal herniation and mid-line shift to left side (Fig. 5). Further two doses of 0.5 g/kg/dose of 20 % mannitol were given and mannitol induced diuresis replaced with 10 mL/kg normal saline bolus during next 14 h of emergency room stay. For suspected underlying infection ceftriaxone and acyclovir was started.

The child was shifted to PICU for invasive ICP monitoring and ventilation. The opening ICP using intraparenchymal fiberoptic microsensor was 36 mmHg. Mild hyperventilation ($PaCO_2$−30–35), deep sedation was initiated, mannitol 0.5 g/kg/dose every 6 hourly and hypertonic saline rate was increased to 1 mL/kg/h. Vasoactive therapy was started to maintain the mean arterial pressure at 90–95th centile, to maintain CPP. But response to above measures was only transient. Despite these measures the ICP persisted between 30 and 50 mmHg and the CPP below 50 mmHg.

What is the Next Line of Management?

1. Use mannitol in higher dose 1 g/kg
2. Metabolic suppression therapy (Barbiturate coma) or
3. Decompressive craniectomy

Mannitol and osmotic therapy had proved ineffective. The options for raised ICP refractory to osmotherapy and other measures were barbiturate coma, therapeutic hypothermia or decompressive craniectomy [7]. Pentobarbital is used for metabolic coma and is titrated to a 90 % burst suppression (2–6 bursts per min) using an EEG monitor. Despite its efficacy, barbiturate therapy has a variable effect on outcome, and has a high complication rate (hypotension, hypokalemia, respiratory complications, infections, hepatic dysfunction and renal dysfunction) [8]. Facilities for controlled hypothermia are not available at authors' centre. Decompressive craniectomy has been shown to effectively reduce ICP in adults with traumatic brain injury with intracranial hypertension refractory to conventional medical

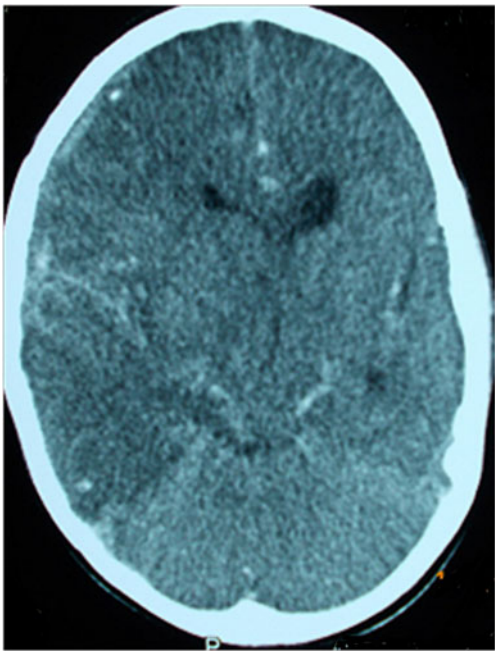

Fig. 5 Axial contrast enhanced CT of the head showing right hemispheric hypodensities with chinking of the ipsilateral lateral ventricle and deviation of the falx cebri

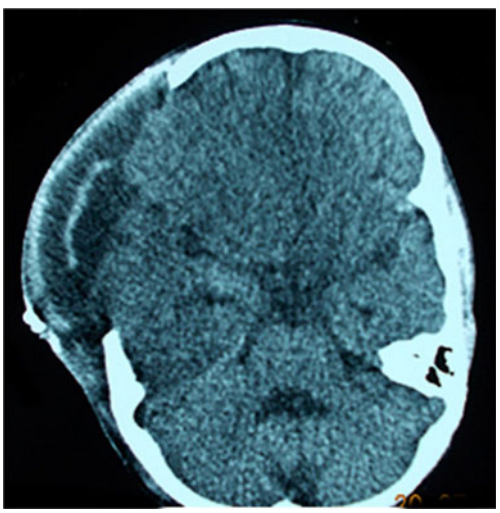

Fig. 6 Postoperative CT head showing bone defect and the herniating brain, reactionary scalp edema and reversal of mass effect

treatment [9]. In view of a clear hemispheric pathology, neurosurgery consult was sought and the patient was taken up for emergency hemicaniectomy. Postoperative course was uneventful (Fig. 6). Osmotherapy was stopped. The patient was successfully extubated on fourth post-operative day and discharged on 14th post-operative day.

Discussion

Decompressive craniectomy effectively increases the volume that the brain can occupy under the scalp. Swollen brain tissue herniates outward through the craniectomy defect; intracranial pressure is immediately lowered, and cerebral blood flow and tissue oxygenation is restored and ischemic damage is minimized. A large craniectomy defect is critical to prevent external brain tamponade. Bifrontal craniectomy is used for diffuse brain edema and fronto-temporo-parietal craniectomy for unilateral lesions. The latter was used in index patient. Decompressive craniectomy has been shown to reduce mortality and improve functional outcome in patients with traumatic brain injury [9]. Reports of its use in children with encephalitis have shown benefit [10]. It is a valuable alternative treatment option in uncontrolled ICP refractory to other measures. The immediate post-operative care includes: 1. Avoiding direct pressure on the craniectomy side; 2. Craniectomy site should be covered for 1 wk (until there is complete skin closure); 3. Patient should be closely observed for: subgaleal fluid accumulation, turgor of the flap and CSF leaks and finally the patient should be helmeted at PICU discharge. All these precautions were taken in the index patient.

Clinical Pearl

Decompressive craniectomy is an important treatment option for the management of patients with medically refractory elevated intracranial pressures. Early and aggressive use of this method may improve outcome.

Contributions PS conceptualised the article. All authors had substantial involvement in contribution of case, draft writing and final approval of draft. PS will act as guarantor for this paper.

Conflict of Interest None.

Role of Funding Source None.

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