

## Clinicopathological Conference Report

### Reye's Syndrome or Primary Mitochondrial Disorder: A Diagnostic Dilemma

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*This case was discussed on 25th January 2012 as a staff clinicopathological exercise at PGIMER Chandigarh, India*

#### Clinical Protocol and Case Analysis

A 7-month-old male child (resident of Ambala, Haryana) was admitted at PGIMER with complaints of fever, cough, rapid breathing and altered sensorium for the last 2 days. He was apparently well 2 days back, when he started to have fever, which was mild-to-moderate grade, intermittent type, not associated with rigors and was responding to antipyretics. Fever was accompanied with a nonparoxysmal cough followed by rapid breathing along with subcostal retractions. Child also developed drowsiness/altered sensorium which was preceded by an episode of doubtful seizure. There was no history of any rash, skin discoloration, pyoderma, ear discharge, loose stools, oliguria, jaundice or bleeding from any site.

There were no major illness or any admission to hospital in past. He was the only child in family and there was no history of any consanguinity or infant death in family. He was a product of full-term normal vaginal delivery at village PHC with normal birth weight. Child was developmentally normal for his age and his immunization was complete for his age. He was on breast milk till 7 months and no weaning was started yet. There was no history of use of any copper utensils in the family.

#### Examination

*At admission:* Pulse-118/mt, RR-38/mt, BP-96/60 mm Hg, with peripheries warm and pink. Anthropometry-weight 8 kg, length 63 cm, OFC 43 cm, which was normal for the age. At admission, child had GCS of E4M3V1, AF at level, normal pupil and SpO<sub>2</sub> at room air was 97%. There was mild pallor, but no icterus, cyanosis, clubbing, edema or lymphadenopathy. He had rounded chubby face, but there was no apparent facial dysmorphism. Blood sugar at admission was found to be low, for which dextrose bolus was given, so it rose to 174 mg%. Systemic examination revealed hepatomegaly of 10 cm below right costal margin,

liver span 14 cm, firm, smooth surface, rounded margins, reaching up to right iliac fosse, splenomegaly (3 cm below left costal margin), but there was no obvious free fluid on examination. On chest auscultation, there were fine crepitations present all over the lung fields. Child was lethargic with brisk DTR's and planters were up going, but there was no focal deficit or any cranial nerve palsy. Cardiovascular system examination was normal.

#### Investigations

	31.10.11	01.11.11
Hb	9.4	7.1
TLC	6,000	11,500
Platelets		3,14,000
	31.10.11	1.11.11
Na/K	139/4.4	139/5.8
BU/Cr	75/0.8	-/0.3

	31.10.11 (5.00 pm)	01.11.11 (3.00 am)	01.11.11 (9.00 am)	01.11.11 (8.00 pm)
pH	7.453	7.45	7.317	7.399
pO <sub>2</sub>	177.6	43.7	100.8	148
pCO <sub>2</sub>	20.4	17.2	35.1	21.4
HCO <sub>3</sub>	13.9	11.7	18.1	12.9
BE	-7.4	-9.2	-6.6	-9.4
SpO <sub>2</sub>	99.6%	80.7%	97.3%	99.2%

*Coagulation profile (31.10.11):* Deranged (PT 36"/14", APTT 36"/25-35", PTI 39%, INR 2.57); CSF examination (01.11.11): Normal (colorless, cells-nil, protein-36 mg%, sugar-42 mg%, Gram stain-negative, C/S-Sterile); card test for malaria-negative.

*Radiology:* Chest X-ray (31.10.11): Cardiomegaly present with congestion of lung fields; ultrasound abdomen-liver span (13.1 cm); mildly heterogenous echotexture, normal IHBR, normal GB, CBD obscured due to gas, normal venous system; right kidney 7.74 cm; left kidney 7.2 cm, normal echogenicity; spleen 8.34 cm size; no free fluid.

**Impression:** Hepatosplenomegaly with mildly enlarged B/L kidneys.

**Course and management:** Child was started on Inj ceftriaxone for his pneumonia. For low blood sugar at admission, dextrose bolus was given and for low GCS and poor respiratory efforts, child was intubated and kept on manual IPPR. After 12 hours, it was changed to ET-T piece for maintenance of airways. The child showed improvement in respiratory rate and distress along with improving sensorium. Thereafter the child was extubated, put on nasal prong CPAP and IV antibiotics continued. Blood sugar was within normal limits and maintenance fluids continued. He was afebrile and hemodynamically stable. Efforts were made to find out the cause for the hepatosplenomegaly and investigations were planned. But unfortunately, after nearly 34 hours of hospital stay, child developed sudden cardiac arrest for which CPR was started. Patient received 3 doses of adrenaline, calcium bolus and Dx bolus (RBS after bolus was 450 mg%). CPR was done for 30 minutes but he could not be revived. Cause for sudden cardiac arrest could not be explained.

PM liver biopsy (02.11.2011) [Biopsy no: S-16987/2011]: Liver biopsy shows maintained lobular architecture diffuse macro- and microvesicular steatosis. The portal tracts are unremarkable. Overall features are of fatty liver. **Impression:** Steatosis.

**Unit final diagnosis:** Pneumonia with sepsis with underlying storage disorder.

## CASE ANALYSIS

In database we had a 7-month-old child, who was admitted to PGIMER, with short pneumonia like illness; he was developmentally normal for his age; examination showed large hepatomegaly and mild splenomegaly; investigations revealed a deranged coagulation profile and ultrasound suggested mild renomegaly. He also had hypoglycemia at presentation, CSF examination was normal and child suddenly died of cardiac arrest. Postmortem biopsy showed steatosis.

The questions which need answers in this case are:

- What was the acute illness for which child was brought to hospital?
- Was there any underlying chronic illness?
- What could be the cause for sudden death?

Acute illness looks like a pneumonia like illness probably with sepsis. The possible explanations for presenting hypoglycemia could be: (i) Poor intake, as child was sick and probably not taking enough (renal parameters also support prerenal azotemia), (ii) it could be a part of sepsis, (iii) it is also possible that hypoglycemia could be a

presenting manifestation of some underlying chronic illness. The most apparent finding in this child was a huge hepatomegaly (10 cm below costal margin), which probably can never occur with just 2 days illness. If we look at causes of hepatomegaly in infancy, there is a big list but pertaining to this case, the following cause must be considered as follows:

1. **Infection:** Viral hepatitis A, B, C, D, E, TORCH infections, congenital tuberculosis, HIV, malaria, kala azar, leptospirosis, fungal, brucellosis, rickettsial infections.
2. **Hemolytic anemia and myeloproliferative disorders:** Juvenile CML, myelofibrosis, osteopetrosis.
3. **Infiltrative disorders:** (a) Hepatoblastoma, hemangio-endothelioma; (b) leukemia, lymphoma, neuroblastoma and (c) histiocytosis (LCH), hemophagocytic lymphohistiocytosis (HLH).
4. **Storage/metabolic disorders:** (a) Glycogen–glycogen storage (I, III, IV, VI); (b) lipid–Niemann–Pick, Gaucher’s, gangliosidosis; (c) protein–tyrosinemia, A1AT deficiency; (d) galactosemia; (e) metal–Indian childhood cirrhosis; (f) mucopolysaccharidosis, hemachromatosis, cystic fibrosis, amyloidosis.
5. **Reye’s syndrome or Reye’s like illness.**

Among infectious causes, congenital TORCH infections could be a possibility in presence of hepatosplenomegaly and seizure like illness, but in absence of any growth retardation, microcephaly, rash or developmental delay, this possibility seems unlikely. Congenital tuberculosis and HIV infections can present with hepatosplenomegaly, but there was no lymphadenopathy, previous illness, prolonged fever, that makes this too unlikely. Hemolytic anemia’s and myeloproliferative disorders cannot be considered in this case, as they present primarily with splenomegaly rather than hepatomegaly.

Neoplasms of liver, as such are very rare in children (1%) and hepatoblastomas are commonest among them, they can present in children below 3 years with a large asymptomatic abdominal mass. But in absence of no other features suggestive of malignancy and no space occupying lesion on ultrasound, that possibility seems very unlikely. LCH usually presents with multiorgan involvement like skeletal system, otitis media, skin and lymphadenopathy, which was not there in this child. To diagnose HLH, we need to fulfil certain diagnostic criteria; this child had fever, splenomegaly and Hb below 9 g/dl. In absence of other investigations, although it is difficult to rule out HLH, but seems unlikely. Among storage disorders; presence of triad (hepatomegaly, hypoglycemia and renomegaly) points toward glycogen storage disorders. GSD-I (Von Gierke’s disease) is due to deficiency of glucose-6-phosphatase,

which leads to accumulation of glycogen and fat in liver and kidneys (gross hepatomegaly and renomegaly). Usually presents at 4 to 6 months with hypoglycemia, hepatomegaly, hyperlipidemia and seizures. They do have doll like faces with fat cheeks, thin extremities and protuberant abdomen. GSD's are not uncommon in Indian scenario, they have been reported from different part of India with mean age of presentation around 15 months. GSD-III, IV and VI also have similar presentations, but GSD-III does not have any renal involvement and type-VI is a milder illness. So, glycogen storage disorder seems a very likely possibility in this child. Only odd thing for this diagnosis will be the post-mortem biopsy report which showed micro- and macro-vesicular steatosis. Although the liver biopsy in these patients is very typical because of presence of storage cells, but hepatic steatosis may develop secondary to abnormalities in any lipid and/or glucose metabolism.

In Neimann-Pick disease, there will be accumulation of sphingomyelins leading to gross hepatomegaly, lymphadenopathy and psychomotor retardation. Type B can have mild pulmonary involvement; which could be a possibility in this case. Gaucher's usually presents with more of splenomegaly rather than hepatomegaly and there were no bone pain or thrombocytopenia, so seems less likely. Gangliosidosis in absence of facial dysmorphism, skin changes, neurological symptoms is unlikely.

Hereditary tyrosinemia type I, which is due to accumulation of tyrosine in liver, kidney and peripheral nerves can present at 2 to 6 months with hepatomegaly, hypoglycemia and nephromegaly. But they usually have hard and irregular liver, renal nephrocalcinosis and peripheral neuropathy, which was not there in this child. Still, this possibility could be entertained. Galactosemia seems unlikely as child was gaining weight normally till 7 months of age, but a partial enzyme deficiency cannot be ruled out. Indian childhood cirrhosis can never present with such a huge liver at 7 months and there was no history of any use of copper utensils in family.

Reye's syndrome or Reye's like illness is a potentially fatal disease, which can present with multiorgan involvement (liver, brain) with a short history. Hypoglycemia could be a presenting manifestation; although the cause for Reye's remains unclear—linked with aspirin use or related to some viruses. It can cause fatty liver (steatosis) and there could be slight kidney enlargement. Jaundice is usually not present, but liver functions are usually altered. Everything fits in this child except a huge hepatomegaly, which is not a common feature of Reye's syndrome.

Possible explanations for cause of sudden cardiac arrest in this child could be:

- An episode of hypoglycemia, as he had previous episodes of hypoglycemia and we are suspecting GSD in this child. But there were normal glucose records in last 24 hours and blood sugar after bolus during resuscitation was 495 mg%.
- Cardiac arrhythmia; possible, if there was some cardiac involvement also, but previous ECG few hours back was normal.
- Electrolyte imbalance (hypokalemia/hyperkalemia) may be considered, but last ECG was normal.
- Intracranial bleed could be a possibility as coagulopathy was present, but there was no active bleeding from any other site or any focal deficit as such.

## FINAL DIAGNOSIS

### Diagnosis

- Pneumonia (community acquired) with sepsis
- Huge underlying hepatosplenomegaly, possible etiology: Storage disorder
- Most likely—glycogen storage disorder I or III and less likely—Niemann-Pick/tyrosinemia/galactosemia or Reye's syndrome or Reye's like illness.

### Cause of Death

- Sudden hypoglycemia
- Intracranial bleed

### Open House Discussion

Dr BR Thapa commented that the investigations were scanty; however, the postmortem liver biopsy showed both macro/microvesicular steatosis with few causes. The most important cause is mitochondrial cytopathy where the child presents with infantile cholestasis, massive hepatomegaly, and an acute liver failure like picture along with extrahepatic manifestations like splenomegaly, cardiomegaly and CNS manifestations just like the way this child has presented. Further on, the hypoglycemic attacks and the acute presentation further stands for this diagnosis. This seems more like a primary mitochondrial cytopathy. Reye's syndrome is a secondary mitochondrial cytopathy and its hallmark is microvesicular steatosis but it still remains a possibility.

Dr S Singhi commented that this seems to be an acute illness with a 2-day history of fever, cough and respiratory distress with cardiomegaly and congested lungs on X-ray chest and so primary myocardial disease like myocarditis presenting with acute cardiac failure, hepatomegaly and congestive splenomegaly should be considered. However, an echocardiogram could not be done. A large liver can

occur in congestive cardiac failure in 2 to 3 days time, but such a large spleen is difficult to explain. Among the glycogen storage disorders, it fits in most classically with GSD type 1 with renomegaly and hepatomegaly. But sudden deterioration and death without previous history of hypoglycemic seizures and failure to thrive is very odd. Dr P Singhi commented that the history and a large liver in infancy suggested a glycogen storage disorder, lysosomal storage disorder or mitochondrial disorders. The liver biopsy however, should have picked up the storage disorder if it was present. Micro/macrovacuolar steatosis has been described as a nonspecific finding in many cases with sepsis and it does not give us a clue. Fundus examination for a cherry red spot seen in most cases of lysosomal disorder was not done. In children less than 1 year of age lysosomal disorders are more common. Mitochondrial disorders can present like this particularly when there is decompensation after infection but the hepatosplenomegaly is not as large as seen in this case. Dr I Panigrahi commented that common chronic liver disorders in childhood are Wilson's disease, glycogen storage disorder and tyrosinemia. Tyrosinemia has a variable presentation and can present as acute liver failure, neonatal cholestasis or as silent cirrhosis. Since there was hepatic and renal involvement, the possibilities kept in this case were GSD type 1 and tyrosinemia. Niemann-Pick was also thought of but liver biopsy was noncontributory. Since PAS-positive macrophages were not documented in the liver biopsy, GSD type 1 still remains a possibility. Hepatic/cardiac involvement with hypoglycemia can be seen in CPT type 1 and CPT type 2. Among the acquired disorders CMV infection, however, should be ruled out. Dr Yashpal Sharma—the cardiomegaly in this case is due to the severe anemia contributed by toxic myocarditis due to the fulminant sepsis.

### Pathology Discussion—PM 24536— Prof RK Vasishtha

A complete autopsy was performed on this 7-month-old male child on whom a clinical diagnosis of glycogen storage disorder Niemann-Pick disease and tyrosinemia was considered. The body weighed was 8 kg. The pleural/peritoneal cavities yielded 200/300 ml respectively of straw colored fluid. The postmortem liver biopsy (S-16987/11) revealed a panlobar fatty change which was predominantly macrovesicular with areas of microvesicular steatosis or a combination of both. The hepatocytes were large balloon like, there was no fibrosis or inflammation but architectural disarray was prominent due to the extensive fat accumulation. No storage cell was identified. At autopsy the liver (Fig. 1A) was markedly enlarged and weighed

800 gm as against a normal weight of 200 gm at this age. The coronal slices were pale and very greasy to feel. On microscopic examination there was a diffuse panlobar steatosis (Fig. 1B) macrovesicular (predominantly), microvesicular and a combination of both as seen on the biopsy. The portal tracts were within normal limits and there was no fibrosis, bile duct proliferation or any inflammation. Stain for PAS was negative, that is, there was no glycogen present in any hepatocyte and there were no PAS-positive macrophages. No storage cell, i.e. either Gaucher's or Niemann-Pick cell could be identified. No features suggestive of tyrosinemia, fructosuria or galactosuria could be seen. Oil red O stain for neutral fat revealed a very extensive fat accumulation in the hepatocytes (Fig. 1C) which were bloated and balloon like. Electron microscopy (Fig. 1D) revealed mitochondria of abnormal shape, size, with lucent matrix and distorted cristae. The kidneys were enlarged, pale and swollen weighing 78 gm (N-60 gm). Cut section revealed a prominent corticomedullary junction. On microscopic examination the tubular epithelial cells were large and bloated up with extensive small vacuolations (Fig. 2A) in the cytoplasm. The glomeruli, vessels and interstitium were within normal limits. Oil red O stain (Fig. 2A inset) for neutral fat showed extensive fat accumulation in the tubular epithelial cells and focally in the glomeruli. Heart was enlarged weighing 65 gm (N-20 gm) with normal valves and chambers. Microscopy revealed normal cardiac myocytes (Fig. 2B) but the oil red O stain for neutral fat revealed extensive fat accumulation in the cardiac myocytes (Fig. 2B, inset). The lungs weighed 115 gm, the pleura was dull, cut section was subcrepitant, rubbery to feel with lower lobe consolidation. On microscopic examination (Fig. 2C) interstitial pneumonia, with diffuse alveolar damage, i.e. hyaline membrane formation (Fig. 2C, inset), alveolar hemorrhage and edema were present. Oil red O stain revealed mild fat accumulation in the macrophages. Brain weighed 860 gm (N-700 gm) and showed marked edema (Fig. 2D) both grossly and microscopically. Spleen weighed 43 gm (N-20 gm), was enlarged with red pulp congestion. Skeletal muscle was normal on morphology and no ragged red fibers were seen on trichrome stain. Oil red O stain revealed mild neutral fat deposition. Electron microscopic examination revealed mitochondrial abnormality. Rest of the organs, i.e. GIT, adrenals, pancreas, etc. were within normal limits.

Final autopsy diagnosis PM 24536, 7 months male:

- Reye's syndrome with marked cerebral edema and extensive fat accumulation in liver, kidneys, myocardium and focally in lungs.
- Electron microscopy—mitochondrial abnormalities in liver.

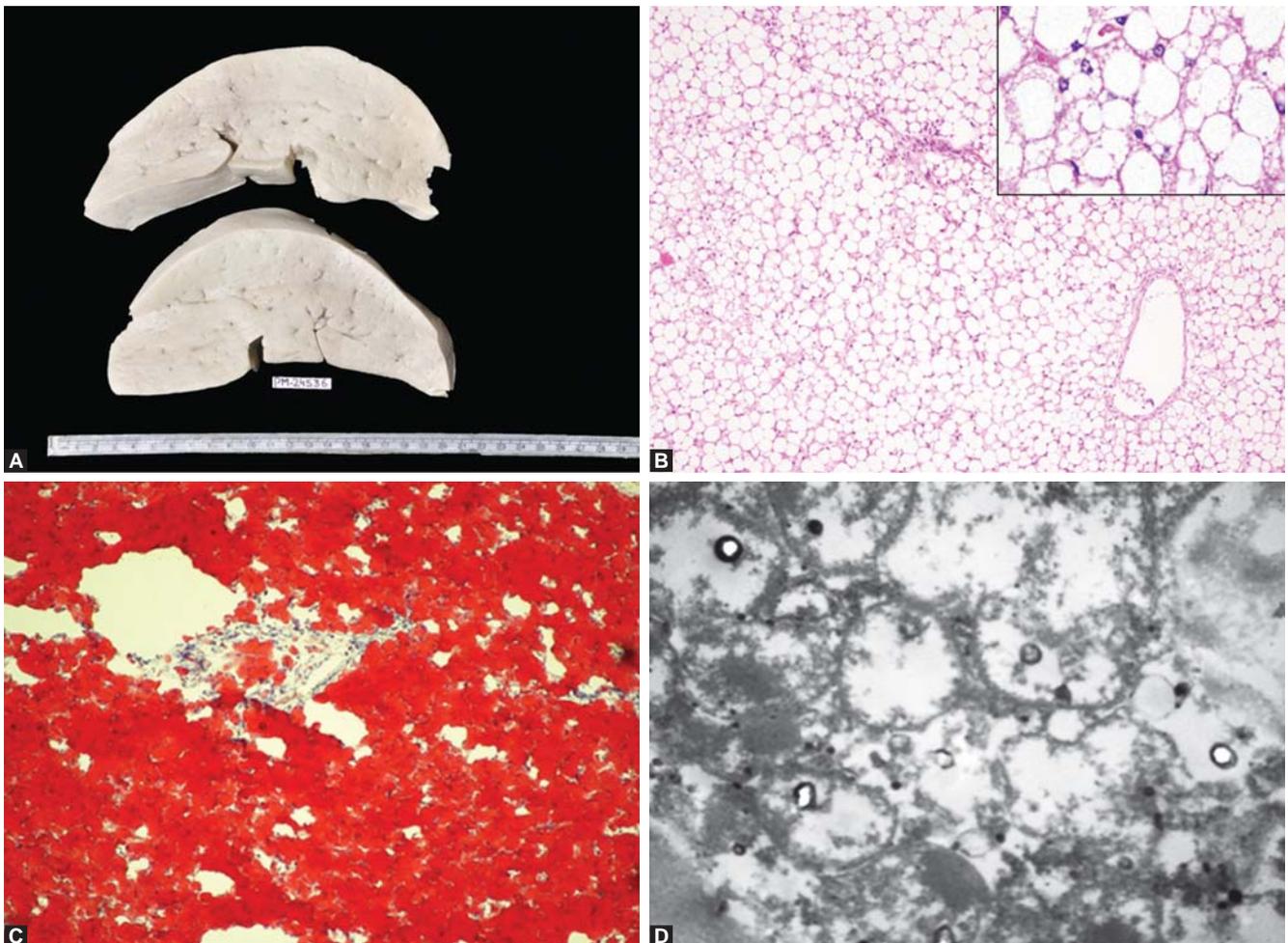
- Interstitial pneumonia, diffuse alveolar damage and pulmonary edema.
- Pleural and peritoneal effusions.

### OPEN HOUSE DISCUSSION

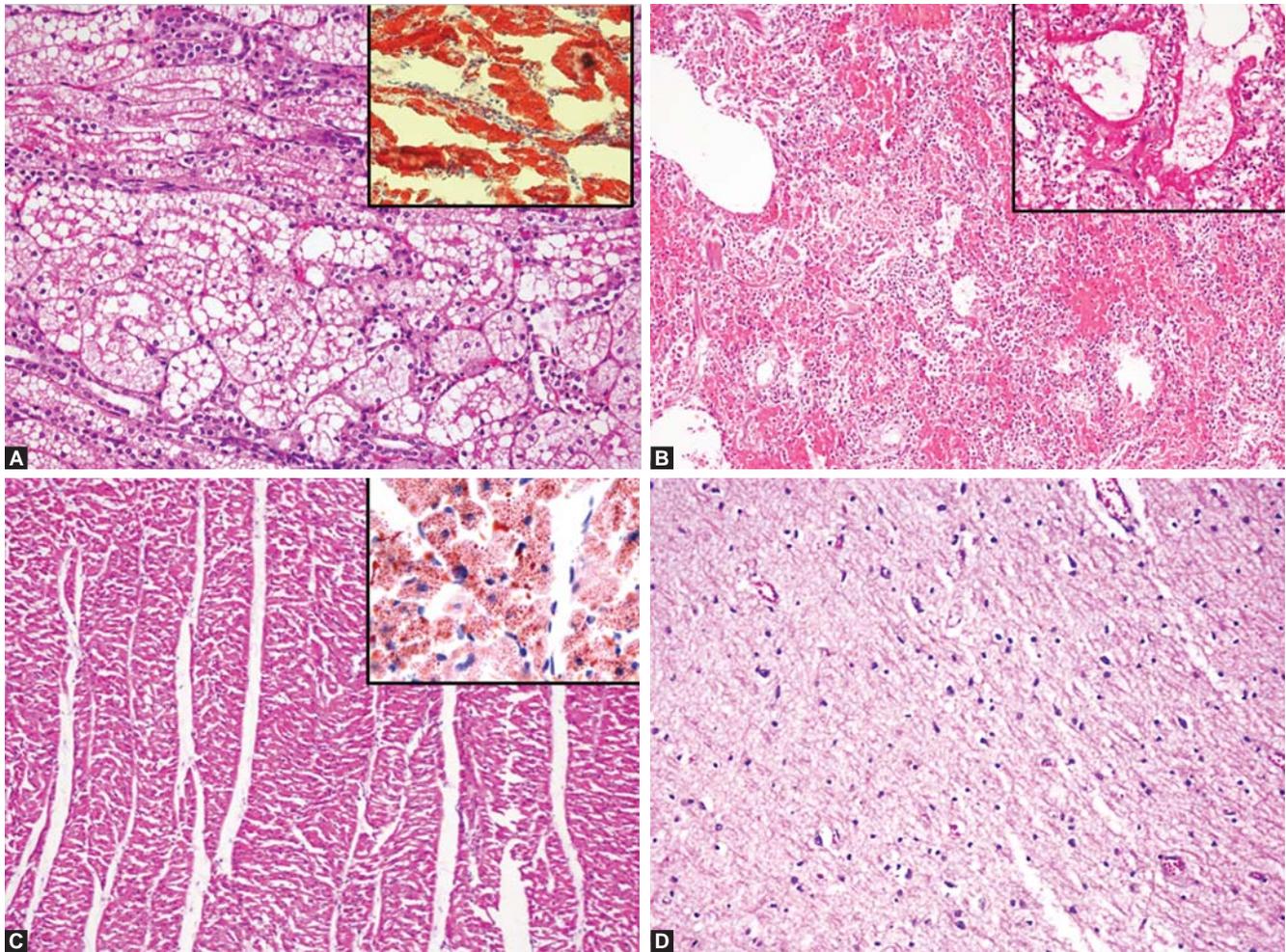
- *Dr BR Thapa:* The hallmark of Reye's syndrome is the classical microvesicular steatosis rather than macrovesicular steatosis or a combination. The latter are, however, seen classically in primary mitochondrial disorders which I think this case fits into. In these disorders there is a defect in the oxidation and phosphorylation of fatty acids as a result of which huge quantity of fat gets deposited in multiple organs like liver, kidneys heart, etc. Reye's syndrome is a secondary mitochondrial disorder in which there is a mutation of nuclear DNA. Here the people live on normally till there is a trigger in the form of some infection, aspirin/valproic acid intake etc. So I think this is a primary mitochondrial disorder in which severe infection led to the demise of the patient.

- *Dr P Singhi* agreed that this was most likely a primary mitochondrial disorder because of heavy, predominantly macrovesicular steatosis in the liver and other organs like kidneys and heart. Reye's syndrome is said to not occur anymore and there are many editorials stating the reasons for that.

*Dr S Singhi* opined whether this was primary Reye's syndrome or a Reye's like syndrome which has been described with 25 different types of metabolic disorders. She referred to an epidemic of Reye's syndrome 12 years ago with over 50 cases, in whom autopsy was done on 12 to 13, all of who had similar features. These cases presented in October until mid December. They had presented acutely with a history of 2 to 3 days and few of them had seizures. There was a mild elevation of both enzymes and bilirubin. In those patients even after extensive investigations no virus or any metabolic disorder could be identified. Similar episodes of Reye's syndrome were seen in UP where they were said to occur due to some toxins in a type of



**Figs 1A to D:** (A) Coronal slices of the enlarged liver which are pale and greasy to feel; (B) microphotograph of the liver showing diffuse macrovesicular steatosis (H and E, 10x) with inset showing macro- and microvesicular steatosis at higher magnification (20x); (C) oil red O stain showing extensive deposition of neutral fat in the hepatocytes (Oil red O stain, 20x); (D) electron microscopy shows increased number of mitochondria of abnormal shape, size, with lucent matrix and distorted cristae (EM x 61800)



**Figs 2A to D:** (A) Microphotograph of the kidney showing bloated up tubular epithelial cells with extensive small vacuolation in the cytoplasm (H and E, 20×) with inset showing extensive deposition of neutral fat in the tubular epithelial cells of the kidney (Oil red O, 20×); (B) microphotograph of the heart showing unremarkable myocardium (H and E stain, 10×) with inset showing extensive deposition of neutral fat in the cardiac myocytes (Oil red O, 20×); (C) microphotograph of the lung showing extensive alveolar hemorrhage and interstitial pneumonia (H and E, 10×) with inset showing diffuse alveolar damage with hyaline membrane formation (H and E, 20×); (D) microphotograph of the brain showing extensive edema (H and E, 20×)

vegetation grown and eaten in that area. She opined that the index case was a Reye’s like syndrome and not necessarily a primary mitochondrial disorder.

- *Dr I Panigrahi* favored a chronic process possibly a Reye like disorder with an underlying metabolic disorder. Fatty acid oxidation defects, such as the short chain acyl CoA dehydrogenase deficiency can have a variable presentation with axonal neuropathy or cardiomyopathy. CPT2 deficiency may be considered where there is macro/microvesicular steatosis and the child presents with hepatosplenomegaly and hypoglycemia. This case does not appear to be a primary mitochondrial disorder as they do not present with hepatosplenomegaly but rather with myopathy or cardiomyopathy with multisystem involvement.
- *Dr RK Vasishta:* Obviously in this case the large size of the liver which was misleading. We tried to exclude any storage disorder affecting the liver but we could not find

anything except neutral fat. The point is, can Reye’s syndrome have such a large liver? Well, there are reports which say so. Although microvesicular steatosis is classical of Reye’s, predominant macrovesicular steatosis or a mixture of the two has been described in literature. Mitochondrial abnormalities on electron microscopy were found in the liver and skeletal muscle. There was no chronic illness/myopathy in this child for the 7 months that he lived and this first acute event led to his demise. So to my mind this fits in more with Reye’s syndrome rather than a primary mitochondrial disorder.

### COMMENTARY

The differential diagnosis in this case is Reye’s syndrome vs a primary mitochondrial disorder. This child was absolutely normal for the 7 months that he lived and he presented acutely with fever, cough, rapid breathing and altered sensorium. An acute event, macro/microvesicular

steatosis, brain edema, oil red O stain showing extensive deposition of neutral fats in the liver, kidney and myocardium and mitochondrial abnormalities in the liver points toward a diagnosis of Reye's syndrome which comes under the category of secondary mitochondrial disorder. A predominant macrovesicular steatosis and such a large liver as seen in the index case can occasionally be seen in Reye's syndrome.

Reye syndrome is named after Dr R Douglas Reye who published the first study in *Lancet* in 1963. It is a rare and a potentially fatal, acute disease of childhood that presents as an encephalopathy which may progress rapidly to irreversible coma and death. It affects children in the age range of 4 to 14 years age and is generally preceded by a viral illness. The disease has decreased dramatically since its association with salicylate use was described and warnings issued about the use of salicylates in febrile children. The disease has a biphasic clinical course with an initial febrile illness, usually associated with upper respiratory infection, followed by apparent recovery and then the abrupt onset of protracted vomiting, delirium and stupor. The basic damage seems to be a widespread mitochondrial injury (secondary mitochondrial disorder) especially in the liver, brain and muscle leading to abnormal metabolism of lipids. Liver dysfunction is manifested by elevation in the transaminases, hypoprothrombinemia and hyperammonemia. Hypoglycemia may be present. Serum amino acid and free fatty acid levels may be elevated. Grossly the liver is enlarged and is yellow to pale due to increased parenchymal lipid. Microscopically the hepatocytes appear either normal or show a classical microvesicular steatosis which is the hallmark of Reye's syndrome. However, at times a combination of both micro/macrovesicular steatosis and occasionally a predominant macrovesicular steatosis can be seen. Characteristically there is no hepatocellular necrosis or inflammation. The ultrastructural features of microvesicular steatosis and typical mitochondrial abnormalities are considered virtually diagnostic of the syndrome. Fat accumulation is seen in other organs notably the renal tubular epithelium, myocardial and skeletal muscle, lung and pancreatic islets. The brain shows edema and mitochondrial changes similar to the ones seen in the liver.

Primary mitochondrial diseases are a group of disorders caused by dysfunctional mitochondria and are often caused

by genetic or mutations to the mitochondrial DNA that affect the mitochondria function. The subclass of these diseases that have neuromuscular disease symptoms are often called a mitochondrial myopathy. In addition to the mitochondrial myopathies, other examples include diabetes mellitus and deafness (DAD), Leber's hereditary optic neuropathy (LHON), Leigh's syndrome, i.e. subacute sclerosing encephalopathy, neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP), myoneurogenic gastrointestinal encephalopathy (MNGIE), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS), mtDNA depletion, i.e. mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), etc. Symptoms include poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological problems, autonomic dysfunction and dementia. The effects of mitochondrial disease can be quite varied. Mitochondrial diseases as a rule are worse when the defective mitochondria are present in the muscles, cerebrum or nerves because these cells use more energy than most other cells in the body. Mitochondrial disorders may be caused by mutations, acquired or inherited, in mitochondrial DNA (mtDNA) or in nuclear genes that code for mitochondrial components. They may also be the result of acquired mitochondrial dysfunction due to adverse effects of drugs, infections or other environmental causes.

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