International Journal of Pathology; 2006; 4(2): 120-123

Case Report

Reye's Syndrome: Diagnosed on a Postmortem Needle Liver Biopsy in an Unexplained Death

Ambreen Moatasim, Anwar Ul Haque and Humeira Rizwan

Department of Pathology, Pakistan Institute of Medical Sciences, Islamabad.

We report here a case of a 14 year old child whose disease remained undiagnosed till death, when the diagnosis of Reye's syndrome was established via a core needle biopsy of liver done for academic purposes. Although Reye's syndrome is a diagnosis of exclusion, a high index of suspicion is critical for its diagnosis.

Key words: Reye's syndrome, Fatty change, Micro vesicular steatosis, Needle biopsy, Autopsy.

Introduction

Reye's syndrome, often preceded by a viral infection, is a rare but a severe and often fatal disease. Although most cases are reported in young children, no age is barred. Its etiology is unknown but subtle and subclinical defects in urea cycle play crucial role. Death occurs from brainstem dysfunction[1], secondary to herniation and usually compression.

The discovery of cases of inborn errors of metabolism (IEM) with similar manifestations and a sharp decline in the use of aspirin among children has made the diagnosis of Reye's syndrome extremely rare and is now considered to be one of exclusion. A high index of suspicion is necessary for its diagnosis. We report here a case of Reye's syndrome in a 14 years old child whose disease remained undiagnosed till death when the diagnosis was mainly established by core needle biopsy of liver and the presence of other supporting data.

Case Report

A 14 year old girl from Chitral residing in Barah Koh, Islamabad had been in a state of poor health for 1 year. She was having off and on fever (ranging from low to high grade) and productive cough. She was taking antipyretics infrequently for fever. She developed progressive pallor and weakness. For past two months, however, the fever became high grade, associated with rigors, chills and sweating. In the last 20 days she had 6-7 episodes of epistaxis and had one day history of easy bruisability. Her family history revealed that mother had pulmonary tuberculosis 7 years back. The patient was referred to Pakistan Institute of Medical Sciences (PIMS) by another local hospital. On examination, patient was very pale with bruises and petechiae all over body. Chest showed bilateral rhonchi and crepts, more on the right side. On abdominal examination, liver was 8-10cm and spleen was 2 cm below the costal margin. Blood complete picture showed pancytopenia. Her LFTs were deranged with bilirubin of 5.8mg/dl and ALP of 573U/L. APTT was prolonged. Serum albumin was 2 g/dl. Serum LDH was markedly raised (1253U/L). Chest x-ray showed bilateral cavitating lesions. Keeping in view of possibility of tuberculosis and other infections, she was started on injectable steroids, ATT, transamine, zantac and Leflox. She was transfused three packs of red cell concentrates but still her condition did not improve. Her bone marrow aspiration showed dysmyelopoiesis, probably infection related and moderate megaloblastic changes (Figure 1) while trephine biopsy displayed moderate degree of reactive fibrosis with no evidence of infiltration in sections examined (Figure 2). Her behavior altered and she developed urinary and bowel

incontinence. Her condition further deteriorated and she developed respiratory distress for which she was

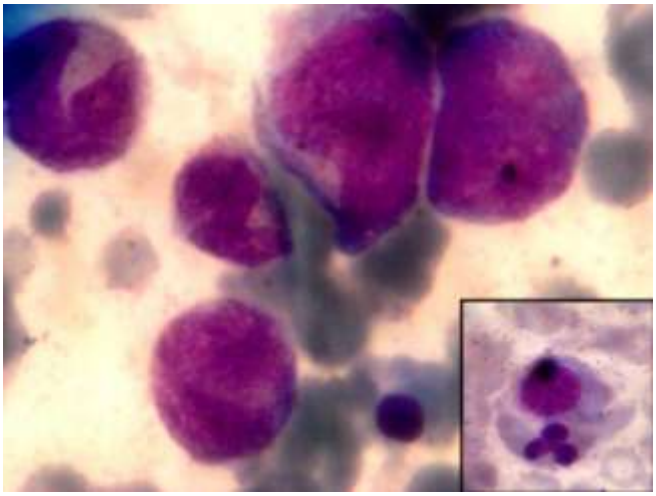

Figure 1: Dysmyelopoiesis and Phagocytosis (Inset) as seen on Bone Marrow Aspiration (Wright Stain X 1000M)

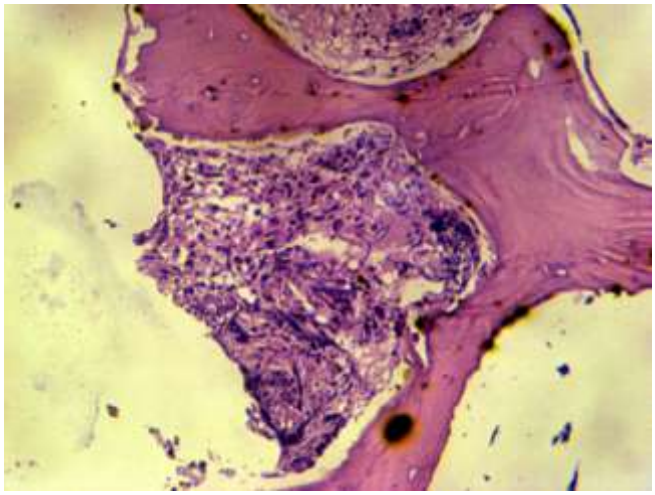

Figure 2: Moderate Degree of Reactive Fibrosis in Trephine Biopsy. (H & E X 200M)

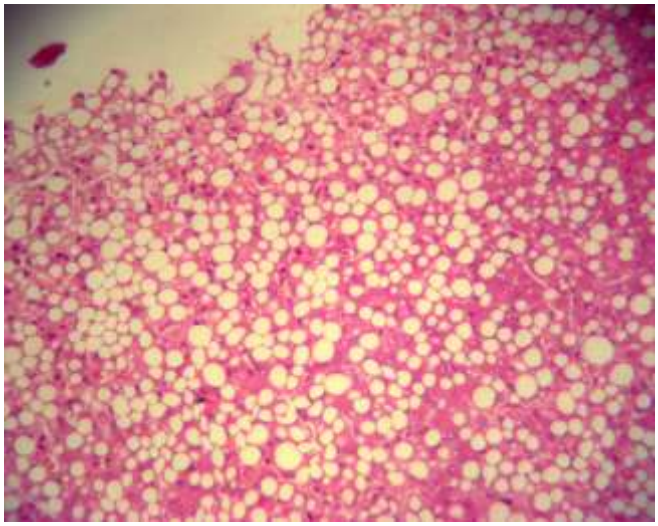

Figure 3: Core Needle Liver Biopsy showing Marked Steatosis (H & E X 200M)

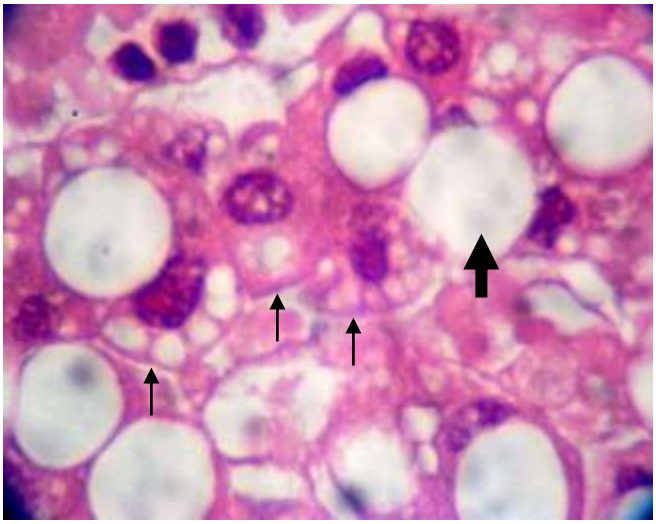

Figure 4: High Power of Liver Biopsy Displaying Both Micro (Thin Arrow) and Macrovesicular Steatosis (Thick Arrow). (H & E X 1000M)

transferred to Medical ICU and put on ventilatory support. However her condition continued to decline with persistent low blood pressure and weak pulse. Her right pupil became fixed and dilated while left was semi dilated and reactive. Due to her worsening status there was suspicion of intracranial bleeding and pulmonary hemorrhage. The patient went into cardiac arrest and died on the same day of being transferred to ICU. Her CPR was not done as she was declared to have a 'Do Not Actively Resuscitate' status. At death, multiple tru cut needle biopsies were taken from lung and liver and sent for fungal and tuberculosis culture as well as for histopathology. The histopathology of liver showed marked steatosis, prominent micro vesicular steatosis alongwith macro vesicular fatty change (Figures 3 & 4), while the lung biopsy only displayed blood clot. As the biopsy was entirely processed and went through alcohol, it felt quite conceivable that if we had done Oil-Red-O stain on cryostat tissue, the microvesicular fatty change would have been much more prominent. Fungal and tuberculosis cultures were both negative. Keeping in view the clinical scenario, lab workup and histopathological findings, we rendered the diagnosis as compatible with Reye's syndrome.

Discussion

Reye's syndrome is characterized by acute non-inflammatory encephalopathy and hepatic failure and was first described as a distinct entity in 1963 by R. D. K. Reye[2]. The peak age of incidence range from 5-14 years, with a median of 6 years.

Although the etiology of Reye syndrome is unknown, it is considered to be multifactorial. The condition typically occurs after a viral illness, particularly an upper respiratory tract infection (URTI), influenza, varicella[3], or gastroenteritis, and is associated with the use of aspirin during the illness. Among other drugs, paracetamol, tetracycline, valproic acid, zidovudine, didanosine and antiemetics have also been associated. A well defined cause-effect relationship between aspirin intake and Reye syndrome in children is not supported by sufficient facts. However, in one of the recent reports, a 10 months old baby treated with aspirin for Kawasaki Syndrome developed Reye's Syndrome[4]. So a question has been hung over the safety of aspirin use in children. The evidence to date is conflicting and non convincing. However, due to the grave nature of Reye's syndrome and the fact that other effective remedies are available, it is recommended that aspirin should not be used in children under 12 years of age unless indicated for childhood rheumatic disease[5]. Toxins like insecticides, herbicides, aflatoxins, paint, hepatotoxic mushrooms have also been implicated. Inborn errors that may mimic Reye syndrome include fatty-acid oxidation defects, amino and organic acidopathies, urea-cycle defects, and disorders of carbohydrate metabolism. Future discovery of other IEMs may ultimately explain even more of these cases. An extensive metabolic workup to exclude IEM must be performed in all cases suspected of Reye's syndrome.

The pathogenesis is unclear, but it appears to involve mitochondrial dysfunction that inhibits oxidative phosphorylation and fatty-acid beta-oxidation in a virus-infected, genetically sensitized host.

As is clear, the manifestations of Reye's syndrome are not unique to Reye syndrome but also seen in other conditions, and given that no test is specific for Reye's syndrome, the diagnosis must be one of exclusion. A high index of suspicion is critical for diagnosis. Centers for Disease Control and Prevention (CDC) have developed criteria for diagnosis of Reye's syndrome and include firstly, the presence of an acute non inflammatory encephalopathy with an altered level of consciousness with no signs in CSF or in brain histology to indicate infection or inflammation. The second criteria is hepatic dysfunction with a liver biopsy showing fatty change or a more than 3-fold increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or ammonia levels and thirdly there should be no other explanation for the condition[6]. Percutaneous liver biopsy may be indicated to exclude IEM or toxic liver disease.Histologic changes include diffuse panlobular microvesicular steatosis in hepatocytes. In brain, edema and loss of neurons while in proximal tubules of kidney, edema and fatty degeneration are usually seen. Ultrastructurally, all cells have pleomorphic, swollen mitochondria that are reduced in number, along with glycogen depletion.

The frequency of this syndrome, that peaked in the 1970s and early 1980s, is now <0.03-1 case per 100,000 persons younger than 18 years[7]. This dramatic decline is largely attributable to the discoveries of and advances in diagnosis of IEM that mimic Reye syndrome and to decreased aspirin use in children. The decrease is most marked in patients older than 5 years. Over reporting of cases during the peak years that did not fully meet criteria and possible underreporting of cases in recent years by physicians who no longer consider the diagnosis, may also account for the apparent decline. Death is usually due to cerebral edema or increased intracranial pressure, but it may be due to myocardial dysfunction, cardiovascular collapse, respiratory failure, renal failure, GI bleeding, status epilepticus, or sepsis.

In our case, the suspected clinical diagnosis was either disseminated tuberculosis or a hematological malignancy but both could not be proven even on thorough investigations. The fact that favors the diagnosis of Reye's syndrome is the sudden onset of the symptom complex that lead to death within a week of presentation. It can be speculated that the child had suffered from a viral infection which was probably superimposed on an inborn metabolic defect that was never suspected and hence never investigated as is usually the case. Also the child had off and on history of intake of antipyretics and as everyone has an easy access to aspirin, this may have been the triggering event. Finally, the liver biopsy showed marked micro vesicular fatty change that further supports this diagnosis. As mentioned earlier, the Reye's syndrome is a diagnosis of exclusion and as no other explainable cause of hepatic and cerebral

dysfunction was found, we strongly suspect that our patient fits into the category of Reye's syndrome which is also supplemented by the findings of liver biopsy. Although the clinical, family and radiological impression of tuberculosis cannot be ignored totally, but we believe that it was not the cause of patient's death as the acuteness of the clinical picture goes more in favor of Reye's syndrome than disseminated tuberculosis. Still further, the findings on liver biopsy were not compatible with tuberculosis.

In summary, early recognition of this condition and treatment are essential to prevent death and to optimize the likelihood of recovery without neurologic impairment. This report also highlights the use of regular medical autopsies to determine the cause of death in undiagnosed cases. Even if the family doesn't permit a complete autopsy due to social beliefs, multiple core biopsies from various tissues can be taken that can be very helpful in reaching an almost accurate diagnosis as in our case. Such medical autopsies can only make us wiser and can change our thought processes so that we could learn from our mistakes. Multiple core needle biopsies or FNACs can be used for different tests other than routine histopathology. This would include histochemistry, immunological tests and electron microscopy. In addition to tissue for routine histopathology, a core may be saved fresh. A serum and urine sample should be obtained if possible and frozen for future testing. This may help in family studies and appropriate management of any detectable metabolic disorder. Also this will make it practical and not impossible to render the diagnosis of Reye's syndrome at an average hospital and by an average physician.[8]

In conclusion, we report a case of Reye Syndrome in an otherwise unexplained, rapid death in a 14 year old patient.

References

1. Schrör K. Aspirin and Reye syndrome: a review of the evidence. Paediatr Drugs. 2007; 9(3): 195-204.
2. Reye RDK, MorganG, Baral J. Encephalopathy and fatty degeneration of the viscera, a disease entity in childhood. Lancet 1963; ii: 749-52.
3. Sullivan-Bolyai JZ, Corey L. Epidemiology of Reye's syndrome. Epidemol Rev 1981; 3: 1-26.
4. Wei CM, Chen HL, Lee PI, Chen CM, Ma CY, Hwu WL. Reye's syndrome developing in an infant on treatment of Kawasaki syndrome. J Paediatr Child Health. 2005 May-Jun; 41(5-6): 303-4.
5. Committee on Safety of Medicines. CSM Update: Reye's Syndrome and Aspirin. Br Med J 1986; 292: 1590.
6. Centers for Disease Control. Reye Syndrome- United States, 1985. CDC Morbidity and Mortality Weekly Report 1986; 35: 66-74.
7. Centers for Disease Control. Reye Syndrome- United States, 1984. CDC Morbidity and Mortality Weekly Report 1985; 34: 13-16.
8. Haque A. Reye's syndrome: an identity crisis. JIMA 1992; 24: 84-7.