Reye Syndrome- An Enigma That Remains

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Reye syndrome was first reported sixty years back by Ralph Douglas Kenneth Reye, Graeme Morgan and Jim Baral in Australia as a non-inflammatory encephalopathy with fatty degeneration of multiple visceral organs with 80% of their patients succumbing to the illness [1]. Gradually it started being reported all over the world. Chandrasekaran, et al. [2] reported a series of nine children (from 1971 to 1973) from Chandigarh who were diagnosed clinically as Reye syndrome. They were the first to report survival of patients suffering from Reye syndrome in India [2]. As time passed, Reye syndrome was managed better and the case fatality rate dropped to 10-20% [3].The exact etiology of Reye syndrome is yet to be understood. However, a strong association with the use of aspirin in the setting of a viral illness was identified. A prompt action in the form of widespread warning against the use of aspirin in febrile viral illness laterled to the disease becoming almost non-existent. It is worthwhile to review the last fifty years as this rapidly progressive fatal disease was made almost non-existent by timely intervention.

THE PAST

Although, reports of illness similar to that of Reye syndrome existed in the literature from 1929, it was first described as a distinct entity by Reye, et al. [1] in 1963. Following this report, small cluster of cases were being reported initially. This clinical entity gained significant attention once an association with aspirin use became evident. The Centre for Disease Control (CDC) established a surveillance system for Reye syndrome in 1968 [4]. Thereafter, 11 to 83 cases were reported annually till 1973. As the disease gained more attention and reporting became better, a peak of 555 cases were reported in 1979-80. The incidence gradually declined with no more than two cases being reported annually from 1994-97 [4]. Similarly, in India, 242 cases of Reye syndrome were reported till 1991 [5].

Reye syndrome is a disorder of the pediatric age group and commonly affects 5-14 years age group [4,5]. The etiology and pathogenesis is not clearly established. Viral infections such as influenza and varicella, toxins such as aflatoxin, pesticides or drugs such as aspirin and valproate have all been implicated. By far the greatest association is with the use of aspirin during viral prodrome. Infection with patho-genic viruses results in an altered immune response with release of various inflammatory mediators that results in damage to the mitochondria. This results in metabolic failure, an arrest in gluconeogenesis and release of toxic metabolites such as ammonia and fatty acids responsible for the clinical presentation. This metabolic failure is accentuated by drugs such as aspirin or other toxins [6]. The controversy regarding aspirin as a causative agent stemmed from the fact that aspirin was being used for a long time before Reye syndrome started being reported. Also, a subgroup of patients of Reye syndrome has no exposure to aspirin. Almost no patient reported from India had exposure to aspirin. Moreover, less than 0.5% of the patients who used aspirin developed Reye syndrome. However, multiple epidemiological studies were carried out and a consistent link with aspirin exposure and development of Reye syndrome was established. We also cannot ignore the fact that reducing the use of aspirin during a viral illness has almost made Reye syndrome disappear [7,8].

Reye syndrome typically presents as a biphasic illness. It begins with a viral illness such as chicken pox, influenza or acute viral gastroenteritis, and several days later there is sudden onset projectile vomiting and altered sensorium that rapidly deteriorates to lethargy, stupor, convulsions and coma. Reye syndrome is a clinical diagnosis and requires fulfilment of the following criteria: presentation as a biphasic illness, cerebrospinal fluid analysis showing less than 10 cell/mm^3, elevated serum transaminases by

200% and serum ammonia by 150%, and exclusion of other causes of encephalopathy and hepatocellular dysfunction [3]. Liver biopsy is diagnostic and helps to differentiate from inborn errors of metabolism (IEM), which mimic presentation like Reye syndrome. It has to be done early in illness to identify the characteristic changes. Light microscopy reveals microvesicular steatosis and absence of necrosis and inflammation. Mitochondrial pleomor-phism and matrical swelling, proliferation of endoplasmic reticulum, a great increase in microbodies and more or less depletion of glycogen can be identified on electron microscopy. In contrast, IEM will have a normally appearing mitochondria [9]. Correction of hypoglycemia with a higher glucose infusion rate and adequate measures to tackle the raised intracranial pressure must be initiated immediately [3].

THE PRESENT

The classical Reye syndrome, which occurs with a prodromal viral illness and an associated aspirin use has almost disappeared, with only a few sporadic cases continuing to be reported. However, IEM such as fatty acid oxidation defects, urea cycle disorders, organic acidurias can masquerade as Reye syndrome. One study reported that 12% of the patients initially diagnosed as Reye syndrome were later found to be having an underlying IEM [6]. Presentation in infancy or toddler age group, as recurrent episodes or an associated family history must raise the suspicion of an underlying IEM.

The larger question that needs to be answered by us is whether the benefits of aspirin withdrawal outweigh the benefits of aspirin use. Aspirin has largely been replaced by acetaminophen. Acetaminophen differs from aspirin in that it does not have anti-inflammatory properties at antipyretic doses. Also, over dosage results in toxic liver injury. Acetaminophen poisoning is the most common cause of acute liver failure in USA. With aspirin over-dosage, toxic liver injury rarely occurs. Aspirin use is still very beneficial in inflammatory conditions such as Kawasaki disease (KD) and acute rheumatic fever (ARF). Reye syndrome has almost never been reported in the setting of these inflammatory conditions (incidence < 0.005%) [6]. By highlighting the risk of Reye syndrome too much, we may be forced to use other non-steroidal anti-inflammatory drugs, which may not be as well tolerated.

Another concern is the increase in the prevalence of childhood asthma. There may be a correlation of early life exposure to acetaminophen and increased incidence of childhood asthma. This has yet to be proven. Likely, changing over from aspirin to acetaminophen has brought about this new dynamic [10].

CONCLUSIONS

In times of coronavirus pandemic, we must be careful in the use of aspirin as prior clustering of cases occurred during epidemics of influenza. One case of multisystem inflammatory syndrome complicated by Reye syndrome has been reported. Care must be taken to utilize aspirin only when absolutely needed. Fear of Reye syndrome should not stop us from using aspirin in conditions such as KD or ARF where its benefits significantly outweigh the risks. The new British guidelines on the management of KD do not mention Reye syndrome as a potential adverse event anywhere in the guidelines as they recognize that the beneficial effect of aspirin outweighs the risk in these conditions.

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