Case Reports

MULTIDRUG - RESISTANT TUBERCULOSIS (MDRTB) IN CHILDREN

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Introduction

The World Health Organization has estimated that 90 million cases of tuberculosis will occur throughout the world in the 1990s and 30 million people will die from the disease [1]. Drug resistance is emerging as a major obstacle to tuberculosis control in the world and is exacerbated by the growing epidemic of Human Immunodeficiency Virus (HIV) [2]. Treatment of drug-resistant tuberculosis is complex, requiring the use of several toxic drugs over 9 to 18 months. Here we present a case of multidrug resistant tuberculosis in a child.

Case Report

A 11 year old child was admitted with complaints of intermittent fever and pain abdomen of 10 days duration. Fever was associated with colicky pain in lower abdomen and constipation. There was no history of haematemesis or malena. The child was treated for endobronchial tuberculosis for 9 months and the treatment had finished in April 98. There was no history suggestive of contact with a case of tuberculosis.

The child weighed 23 kg (< 5th%ile), had pulse of 90/min. temperature 100°F, BP 110/70mm of Hg. There were multiple cervical and axillary lymphnodes of 0.5 cm and 1.0 cm diameter respectively. The abdomen was doughy and tender all over, most marked over right iliac fossa. There was no guarding or rigidity. Liver was palpable 2 cms below the costal margin and the spleen tip was just palpable. There was no free fluid in the peritoneal cavity and bowel sounds were present. Systemic examination was essentially within normal limits.

A diagnosis of subacute intestinal obstruction, possibly due to intestinal tuberculosis was made and symptomatic treatment started. Haemoglobin was 9.2 gm%, TLC 9600/cmm and ESR 16 mm fall in the first hour. Chest X-ray showed hilar adenopathy. USG abdomen showed multiple enlarged mesenteric lymph nodes in para aortic region with minimal free fluid. Mantoux test and blood for HIV was negative. Axillary lymphnode biopsy was done which showed granulomatous changes and hence the child was put on 2 EHRZ+10 HR regime of antitubercular treatment (ATT).

Despite treatment for 25 days the child lost 1 Kg. His haemoglobin fell to 6.8 gm%. He also developed cold abscess in the neck and continued to be febrile with predominant abdominal symptoms of anorexia, pain abdomen and constipation. Cold abscess was drained and sent for culture as well as for ELISA for tubercular antigen and antibody. The ELISA for tubercular IgG was positive with a value of > 1600 IU/ml. In view of persistence of symptoms, recurrent cold abscess, positive IgG and no improvement in general condition, second line antitubercular drug i.e. kanamycin, ciprofloxacin and PAS were added after 6 weeks to the ongoing treatment. The exploratory laparotomy, undertaken due to persistence of constipation, pain abdomen and fever, revealed massive matted mesenteric lympnodes, multiple adhesions and miliary tubercles all over peritoneal surface. Histopathological study of omentum, liver and lymphnodes confirmed the diagnosis of tuberculosis.

After about one month of introduction of second line ATT the child became afebrile and was discharged. He was admitted again after 3 weeks with complaints of headache, fever and vomiting of 3 days duration. The CSF analysis showed protein 50mg/dl, raised globulins, sugar 52 mg/dl and cells 45/HPF (predominant lymphocytes). Hb 6 gm% and TLC was 14200/cmm with polymorphonuclear leucocytosis. Fundus showed early papilloedema. Cerebral decongestive therapy with antibiotics was instituted and second line antitubercular drug ciprofloxacin was replaced by clofazimine. However, the deterioration was very rapid. The child developed left sided hemiparesis with 7th nerve palsy UMN type after 10 days of admission. MRI revealed hyperdensities in left lentiform nucleus, head of caudate nucleus and anterior limb of internal capsule. Three days later he lapsed into coma and subsequently died. The culture and sensitivity report received after 12 weeks revealed growth of *Mycobacterium tuberculosis* and the sensitivity report received later showed resistance to all primary antitubercular drugs.

Discussion

In a report from WHO children less than 15 years of age, represent 1.3 million cases out of which 4,50,000 die annually of tuberculosis [2]. The shift of therapy to outpatient care has resulted in reduced compliance leading to increased rate of treatment failure relapses and acquired drug resistance. There has been a significant increase in the number of cases of MDR-TB in adults but very few reports are available on MDR-TB in children. The first report of drug resis-

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tant tuberculosis was published in 1961 [3].

The definition of multidrug-resistant tuberculosis (MDR-TB) is not standardized. Previously MDR-TB has been defined as resistance to two or more first line antitubercular drugs but recently MDR-TB refers to organisms resistant to Isoniazide (INH) and Rifampicin (RMP) with or without resistance to other drugs [4].

There are two major types of drug resistance. Primary resistance occurs when an individual is infected with *Mycobacterium tuberculosis* that is resistant to the drugs at the time of initiation of therapy. Secondary resistance occurs when drug resistant organisms emerge as the dominant population during therapy. Major causes of secondary drug resistance of *Mycobacterium tuberculosis* are poor compliance by the patient and poor management by the physician. The pattern of primary drug resistance seen in children parallels to those found in adults in the same population [5].

There are no published series of multi drug resistant tuberculosis in children due to their inability to produce sputum and non availability of specialized investigations and more sensitive culture technique. In children, it is primary resistance as in most instances they acquire their infections from adult source with resistant bacteria. Secondary resistance has been presumed when symptoms return after initial relief. This child was treated for endobronchial tuberculosis for nine months and presented again with features suggestive of intestinal tuberculosis. In the absence of detectable source of tuberculosis in close contact, it may well be presumed to be a case of secondary resistance.

Drug resistant bacilli are the consequence of human related factor be it the physician or the patient. Spontaneous mutations and genetic basis of this mutation has also been discovered. Mutations in katG, inhA and ahpC genes are found in up to 90% of isoniazid resistant strain. Rifampicin resistance is associated (> 96%) with rpoB mutations. Pyrazinamide resistance with pncA mutations (72-97%). Ethambutol resistance with mutations in embB (47-65%). Streptomycin resistances with rrS or rpsL mutations (70%) and flouroquinolone resistance with gyrA substitutions (75-94%)[6].

A study in New Delhi Tuberculosis Center revealed initial resistance to INH in 18.5% and to RMP in 0.6% cases [7]. In various other studies resistance to INH or RMP and both drugs vary from 3% to 33% and to four first line drugs (INH, RMP, SM, EMB) was seen in 6% cases [8]. In 1994, CDC surveys of drug resistant isolates, 18.9% of isolates from children with TB were resistant to one or more drugs [9]. On clinical suspicion of resistant TB in this case second line drugs were added pending receipt of sensitivity report.

The use of radiometric technique such as BACTEC (Becton Dickinson Diagnostic Instrument Systems. Towson. MD) can reduce the time of isolation, identification and drug susceptibility testing of tuberculosis to as few as 3 to 4 weeks as opposed to prevailing 9 to 12 weeks [10]. Unfortunately rapid diagnostic methods are not readily available.

MDR-TB is difficult and expensive to treat. The management of MDR-TB requires familiarisation with second line antimycobacterial agents. These drugs are generally less potent, poorly tolerated and frequently more toxic than INH and RMP. MDR-TB therapy must be individualised and based on susceptibility studies. INH and RMP resistance is frequently accompanied by resistance to other first line drugs and a history of previous antituberculous treatment was found in over 40% cases [11]. Treatment includes at least 3 to 5 agents to which the organism is susceptible in vitro. A combination of INH, RMP and Pyrazinamide (PZA) with the addition of Streptomycin (SM), Ethambutol (EMB) or Ethionamide should be regimen used in most of these children. CDC recommends PZA and EMB to be continued for an additional 12 months [12]. Patients infected with organisms resistant to both INH and RMP require at least 18 months of therapy. Some of these patients die of tuberculosis or continue to have active tuberculosis despite optimal therapy. The second line drugs to be considered include PAS, Thiacetazone, Cycloserine, Ciprofloxacin, Ofloxacin, Clarithromycin and Azithromycin or Meropneum [13].

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