

Acute Lymphoblastic Leukemia in Association with Long Term Exposure to Trimethoprim-Sulfomethaxazole

Trimethoprim-Sulfomethaxazole (TMP-SMX), a folic acid antagonist, is extensively used for the treatment of pediatric infections. It is clearly known that long term exposure to this drug at high doses is associated with megaloblastic anemia and aplastic anemia(1,2). Antibiotic use is one of the least controlled areas of drug treatment in Turkey where antibiotics are still considered as over-the-counter medications by the majority. Coupled with suboptimal patient education at large, public has easy access to antibiotics through drug stores.

A four-year-old male child presented with a history of anorexia and fatigue for the last several weeks duration. His past medical history was remarkable for an ear infection at six months of age. He was then prescribed TMP-SMX for the treatment of the ear infection. The family noticed that the infant liked the taste of the liquid form of TMP-SMX. The parents continued to purchase the drug for the infant almost in lieu of daily fruit juice replacement. Thus his daily intake of TMP-SMX ranged between 6 to 12 mg/kg per day for TMP and 30 to 60 mg/kg per day for SMX since he was 6 months old. The child was neither followed up after the initial ear infection nor admitted to regular health care services because of his parent's low socio-cultural level. Family history was unremarkable including history of malignancies.

Physical examination revealed a male child with age appropriate growth parameters including weight and height. He displayed mild tachycardia, remarkable pallor, hepatomegaly, and splenomegaly.

Complete blood count revealed severe anemia, normal leukocyte count, and mild thrombocytopenia. Peripheral blood smear revealed lymphoblasts (75% of all white cells) and hypersegmented neutrophils. Biochemical studies revealed low serum levels of vitamin B₁₂ (15 pg/mL) and folic acid (0.5 mg/mL). Bone marrow aspirate revealed L1 morphology by 95%. The diagnosis of pre B cell acute lymphoblastic

leukemia (ALL) was confirmed with flow cytometric analysis. TMP-SMX use was discontinued and immediate treatment for ALL was started.

TMP impairs the function of the dihydrofolate reductase enzyme and inhibits the synthesis of folic acid. Folic acid deficiency particularly affects those hematopoietic cells with a rapid turnover. The chronic decreased levels of serum folic acid due to long-term exposure to TMP may cause megaloblastic anemia and thrombocytopenia. The first striking feature of this case is the development of pre B cell ALL on megaloblastic anemia grounds. In 1992, Islam, *et al.*(3) reported the increased risk of acute and chronic leukemias in patients with long standing megaloblastic anemia. Colagiovanni, *et al.*(4) emphasized megaloblastic anemia to be a risk factor for leukemia and T cell lymphoma. The exact mechanism for development of leukemia due to prolonged TMP-SMX use is unknown. Aberration factors that control hematopoiesis and specific cytokine responses to chemicals that cause megaloblastic anemia may contribute to the development of leukemia(3,4).

The second striking feature of the case is the occurrence of a series of neglect resulting in the present outcome, including the safety and medical neglect at the family level, safety neglect at the society level that set up the stage for the misuse of a drug, and medical neglect at the physician level by withholding proper patient education.

**Orkide Hudaoglu,
Yavuz Tokgöz,**

*University of Dokuz Eylül,
Faculty of Medicine,
Department of Pediatrics, Izmir,
Turkey.*

E-mail: orkidehudaoglu376@hotmail.com

REFERENCES

1. Tapp H, Savarirayan R. Megaloblastic anemia and pancytopenia secondary to prophylactic cotrimoxazole therapy. *J Paediatr Child Health* 1997; 33: 166-167.
2. Kobrinsky NL, Ramsay NK. Acute megaloblastic anemia induced by high-dose trimethoprim-sulfamethoxazole. *Ann Intern Med* 1981; 94:780-781.

3. Islam A. The origin and spread of human leukemia. *Med Hypotheses* 1992; 39:110-118.
4. Colagiovanni DB, Stillman WS, Irons RD. Chemical

suppression of a subpopulation of primitive hematopoietic progenitor cells. *Proc Natl Acad Sci USA* 1993; 90:2803-2806.

Suicides in Children

On the eve of World Suicide Prevention Day on 10th of September, we were shocked to get a child who was only 9 years 7 months old and was admitted in a serious condition for attempted suicide by hanging. With intensive resuscitative efforts and proper supportive care, the child could be saved.

It was revealed that he had been scolded by his mother in the morning for not paying due attention to his studies. But, why this trend? Is this the result of media overexposure of immature brains or the increasing intolerance of kids to parental disciplining methods? Who is more guilty? Is it because of heightened expectations or because of heightened level of intolerance in kids? How far the parents can go to discipline their children? Where are these people supposed to go whenever the need arises? Are adequate counseling facilities available? These are some of the questions we all need to answer.

The President of International Association for Suicide Prevention has said- "In this age of preoccupation with global violence, terrorism and homicides, we often ignore the fact that world-wide more people kill themselves than die in all wars, terrorist acts and interpersonal violence combined(1). WHO says that more than one million people kill themselves every year. Many more millions attempt to do so. A vast majority of these are children. But, given this magnitude, very few studies have been done on this subject especially in India. We could find only one study from India on the suicidal pattern in children(2). It was a 10 years retrospective study which had revealed that the most common age-group for suicide in children was 15-18 years. The youngest child in that study was

11 years old. But, our child was even younger, not even 10 years old. We need to find out the real magnitude of the problem in India.

It is important to translate our knowledge and understanding of suicide to promising areas for suicide prevention. These areas include improving mental health treatment and management, educating physicians, restricting access to lethal means of suicide, educating the community, providing help in crises situations, and providing support for suicide attempts. To prevent such unfortunate incidents, we have to educate the parents so that they seek early help. Physicians also need to be trained adequately so as how to handle such situations. Mental health education should be given more importance in undergraduate and postgraduate courses. Plans should be made to link-up mental health check-ups with regular growth-monitoring. Schools should also be made to pay proper attention to this aspect. Counselors should be appointed in school also. In short, we all need to think over it and act. Our sincere efforts are needed to stop many more young and productive lives getting nipped in the bud in this pathetic yet preventable manner.

Madhumita Nandi,

R.K. Monda,

Department of Pediatrics,

IPGMER, Kolkata 700 020, India.

E-mail. madhumitabanik@rediffmail.com

REFERENCES

1. Statement of the President of International Association for Suicide Prevention. <http://www.iasp.info>
2. Lalwani S, Sharma GASK, Kabra SK, Girdhar S, Dogra TD. Suicide among children and adolescents in South Delhi (1991-2000). *Indian J Pediatr.* 2004; 71: 701-703.