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Case Report

Role of antiepileptics in Lesch Nyhan Syndrome

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Lesch Nyhan Syndrome is an x linked disorder of purine metabolism manifested by mental retardation, hyperuricemia and compulsive self biting. The defect results from enzyme (HPRT) deficiency. There are several neuropsychiatric symptoms depending on the level of HPRT. We present here a boy of 54 months presenting with classical features and treated with three different antilepileptics in successive order. Treatment with Gabapantine had shown significant improvement of neuropsychiatric features in contrast to other antiepileptics.

Keywords: Lesch Nyhan Syndrome, Antiepileptics, Gabapantine.

INTRODUCTION

Lesch Nyhan Syndrome (LNS) is a rare hereditary disorder of purine metabolism caused by a deficiency of the enzyme Hypoxanthine-Guanine Phosphoribosyl Transferase (HPRT) (Lesch and Nyhan, 1964). Epidemiology of the disease in Bangladesh is not known but the incidence seems fairly uniform worldwide at about 1 in 3,80,000 (Olson and Houlihan, 2000). The cardinal features of this disorder are mental retardation, self mutilation, choreoathetosis and hyperuricemia. Defect in neurotransmitters particularly the dopaminergic system is believed to be associated with self-injurious behavior (Mcmanaman and Tam, 1999; Jancovic Jet al., 1988). Therefore punishment or behavioral modification are ineffective and can lead to increase in activity. Several antiepileptics have been suggested for the treatment of LNS in different reports with conflicting results (Harris, 2004; Kemph et al., 1993). The present case is reported to highlight the role of those antiepileptics in the treatment of LNS.

Case Report

Nayeem, a boy of 4 years 6 months got admitted in Khulna Medical College Hospital on 24 March 2010 with the complaints of self-biting, hair pulling and slurring of speech for last two years. According to the statement of mother, the baby was reasonably well up to the age of 2 years. Thereafter, he began to bite himself especially on right hand 10-15 times a day for 2-3 minutes each time (Figure 1). Rarely did he bite other children. The boy also pulled his hair and hit his head by own hand for same duration (Figure 2). These problems had been increasing day by day. The mother also noticed that his speech was gradually becoming indistinct.

He had no history of persistent neonatal jaundice. The boy was born at full term, but there was prolonged labour with birth asphyxia followed by convulsion at second day of birth. He was fed with both breast milk and artificial milk from birth. Mile stone of development was delayed by 6-9 months. There was no history of consanguinity and the family was poor socioeconomically. The child was treated by a Psychiatrist for last six months without any improvement.

On General examination, the child was restless but the nutritional status was average (BMI-19.2) and his occipito-frontal circumference was on 3rd centile line. Multiple bite mark was present on hands specially on right side. Nervous system examination revealed the child as non-cooperative and disoriented with disarthric speech and low intelligence. Cranial nerves and sensory function were normal. In motor function there was paresis of left side of the body along with chorea. He had difficulty in walking with stumping gait. He had no control over bowel and bladder but there was no sleep disturbance.

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Figure 1. Scar of multiple bite marks on hand.

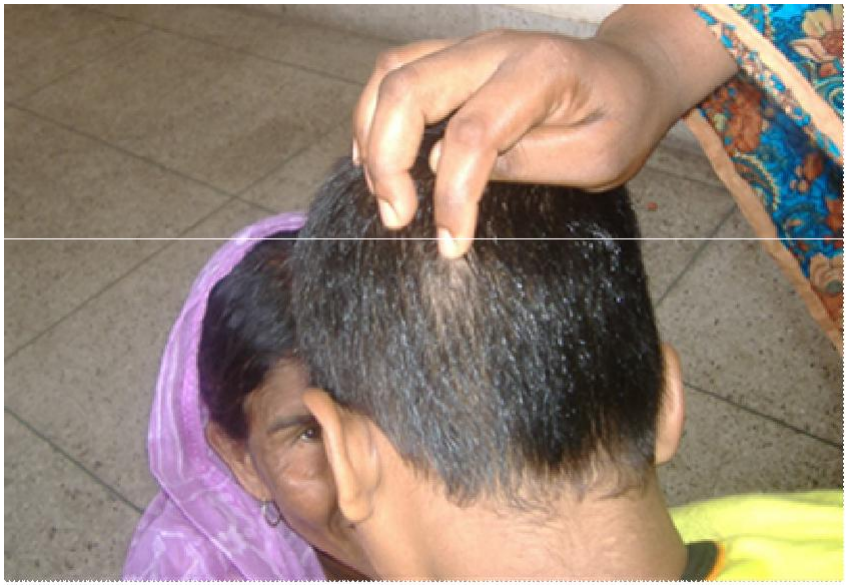

Figure 2. Sparse hair on scalp due to pulling.

Routine investigation findings were normal. CT scan revealed early atrophic changes in cortex. Serum uric acid (7.5mg/dl-0.38mmol/l) was raised (normal limit: 2-6mg/dl). Urinary uric acid: creatinine ratio (6:4) was highly suggestive. The child was treated successively with three antiepileptics and prior to trial written permissions was taken from the parents of the child and also from the ethical review committee of the hospital.

The patient was managed with allopurinol for hyperuricemia. Parents did not agree for teeth extraction. Deep brain stimulation in globus pallidus was beyond our scope. Prevention in the family was attempted by genetic counseling particularly advising for prenatal diagnosis by testing the mother in next pregnancy. Carbamazepine, sodium valproate and gabapentine was tried for three months each and monitoring was done at monthly interval

on behavioral disorders (agitation, biting, slapping, hair pulling, social interaction), extrapyramidal disorders (chorea, dystonia, gait) and autonomic control (bowl and bladder function). Independent behavior assessment scale was used for evaluation of adaptive behavior. It was found that gabapentine contributed in significant reduction of neuropschiatric feature particularly self biting, hair pulling and chorea. Self injurious behavior returned after discontinuation of drug for two days.

DISCUSSION

In 1964 the LNS was first described by Lesch & Nyhan followed by discovery of defective enzyme (HPRT) by Seegmiller in 1967 (Nyhan, 1976). The responsible gene was identified on 1985. It is an x linked condition with a defect at chromosome point Xq26-q27 (Nyhan et al., 2002). There is virtually no HPRT with levels below 1.5% in LNS. However in it's other variant (Kelley-Seegmillar Syndrome) the enzyme level is at least 8%. Various neurotransmitter have been identified to play important roles in the manifestation of self injurious behaviour.

The three main features of the disease are excessive production of uric acid, behavioral disorder and neurological problems- mental retardation, spastic cerebral palsy and choreoathetosis. In infancy, there may be orange sands in nappy due to urate crystals and delay in motor development (Ankem et al., 2000). Behavioral disorder tends to start after second birth day. Testicular atrophy is common and puberty is delayed. Mental handicap is there and IQ typically around 60. Sensory function remains intact but motor skills are grossly impaired. Extrapyramidal features include dystonia, choreoathetosis and opisthotonic spasms and ballismas. Many children show pyramidal features including hyper-reflexia and clonus (Jinnah et al., 2006). Delay in walking is noted, eventually all patients require a wheelchair. Behavioral disorders are shocking. Self injury may result in partial amputation of fingers, tongue and oral mucosa. Compulsive behaviors occur as signs of aggression such as hitting and spitting (Robey et al., 2003). One of the cardinal features of this disorder is self injurious behavior typically beginning around 3 years of age with biting of fingers and lips (Mcmanaman and Tam, 1999).

In LNS uric acid levels in both blood and urine are raised (>7mg/dl), Urinary Urate to Creatinine ratio is >3:4 (Harris, 2004). Blood film shows macrocytic anaemia. Enzyme activity (HPRT in blood (Lymphocyte) / Tissue (Fibroblast) is <1.5% Normal. Brain imaging shows nonspecific changes with diffuse atrophy. Reduced cerebral volume including caudate nucleus may also be noticed.

Differential diagnosis in our case included cerebral palsy, although suggestive from history in this case the motor development was not markedly affected. Autism could be considered for communication difficulties but the child did not have poor eye contact and solitary play (Harris, 2004). In Rett syndrome, the development slows at later childhood but the male sex and absence of extrapyramidal features goes against it (Schretlen et al., 2005). Cornelia de Lange syndrome, a condition associated with mental retardation and self injurious behaviour, is not due to metabolic defect. The principal limitation of this report was lack of genetic study and estimation of serotonin level in blood. Moreover, bioassay of serum carbamazepine and other antiepileptics could not be done due to lack of laboratory facilities.

Reduction of uric acid does not help in reducing self injurious behavior. Various anticonvulsants such as benzodiazepines, clonidine, valproate and carbamazepine are used to reduce the neurological and behavioral problem (Mattson, 1998; Roach et al., 1996). In a study on rats, administration of dopamine agonists resulted in self-biting behaviour (Goldstein et al., 1985). Mcmanaman and Tam used GABA in LNS and observed the decrease in self injurious behavior which might be due to increase in brain GABA levels (Mcmanaman and Tam, 1999; Lloyd et al., 1981). Inspite of well established dopamine supersensitivity hypothesis in animal model, the therapeutic effect of dopamine agonist and antagonist on self mutilation remains equivocal in human case (Olson and Houlihan, 2000; Mcmanaman and Tam, 1999). The present study showed a clear beneficial effect of Gabapantine on LNS while the other two drugs were ineffective. Further trial on a number of patients could be helpful to validate the use of Gabapantene in Lysch Nyhan syndrome.

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