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AN UNUSUAL PRESENTATION OF NEURONONOPATHIC GAUCHERS DISEASE.

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ABSTRACT

A six years old male child presented with tremor, ataxia, speech apraxia, supranuclear gaze palsy and hepatosplenomegaly. There was no history of seizures and psycho-cognitive abnormalities. The clinical and bone marrow findings were consistent with Gaucher's disease type 3.

KEY WORDS: Gauchers disease, Enzyme replacement therapy, Gene therapy, Bone marrow transplant

INTRODUCTION

Gaucher's disease (G.D) is the most common inherited lysosomal storage disorder due to deficiency of acid beta glucosidase1. It is divided into 3 types[1, 2]. Type 1 is a chronic non-neuropathic form of the G.D involving mainly viscera and blood forming cells. Type 2 is an acute neuropathic rapidly fatal form of the G.D presented in infancy. It rapidly progressive leads to death at the age of two years. It presents with dysphagia, persistent head hyperextension, paralytic strabismus, trismus, generalized spasticity and psychomotor regression. Type 3 is a chronic neuropathic form of disease presented mostly in childhood with progressive myoclonic epilepsy, horizontal supranuclear gaze palsy, dementia ataxia, spasticity, while systemic illness tends to be mild[2].

CASE REPORT

A six years old male child presented with difficulty in writing, walking and speaking since the age of 4 years. His problem first came to light when he was sent to school and the teacher noted that his hand shook whilst writing, later on his condition worsened and he kept tripping and falling during walking which eventually progressed to the extend that at the time of admission he was only able to sit up on the chair. His speech has also changed and according to the mother he was slow in initiation of his speech and in completing the sentences. He also tended to break up words while speaking. He had drooling of his saliva and he was gradually loosing weight. There was no loss of consciousness and no episode of reported seizures. He is the 4th issue of consanguineous marriage. There was no family history of similar illness or progressive neurological deterioration. His developmental history had been normal till the age of 4 year. He was born full term by spontaneous vertex delivery and he had been fully immunized.

On examination he was pale, conscious and alert, normal facies and no obvious dysmorphic features. His height was at 10th percentile. His weight was below the 5th percentile. His head circumference was at 10% percentile. His higher mental function seemed normal for his age. His speech was staccato and there was an obvious tremor in his hands which were coarse and aggravated with voluntary movements. Eye examination shows nystagmus and upward gaze palsy and fundus examination was normal. He was hypotonic with brisk deep tendon reflexes with bilaterally up going planters. The remaining cranial nerves were intact and fundus was normal. His liver was 2cm below right costal margin and spleen was 7cm enlarged.

Investigation done including complete blood count which showed microcytic hypochromic anemia. His serum electrolytes, RBS, SGPT, Serum lactic acid, Serum ammonia, and cerulloplasmin and vitB12 level were within normal limits. His urine for reducing substance and ketones were negatives. His X-rays of chest and femur were normal and did not show any dysostosis multiplex. His EEG and EMG/NCV were normal. His MRI showed high intensity signals in peritrigonal white matter bilaterally extending in the supraventricular areas with almost symmetrical appearance. His bone marrow examination showed increased foamy histiocytes that constitute 10% of the

total nucleated cell population (fig 1). In PAS staining foamy histiocytes were seen. The final diagnosis was therefore consistent with Gaucher's disease type 3.

DISCUSSION

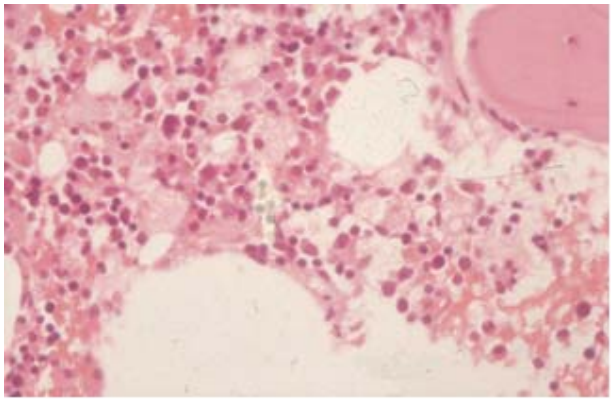
Gaucher's disease (GD) is an autosomal recessive inherited form of lysosomal disorder caused by deficiency of lysosomal enzyme glucocerebrosidase resulting in pathological accumulation of glycolipid in mononuclear phagocytic system[1]. Conventionally it is divided into three clinical phenotypes[1]. Partial deficiency of glucocerebrosidase is associated principally with hepatosplenomegaly, features of hypersplenism, skeletal manifestation and in severe cases; lung is involved, in non neuropathic, type 1 gaucher's disease. Here storage material in macrophages originates from turnover of exogenous glycolipid. Severe deficiency of glucocerebrosidase caused by disabling mutation is additionally associated with neurological manifestation that in part reflects failure to degrade endogenous neuronal glycosphingolipid, the so called type 2 and 3 disease categories[2].

Patient with GD with neurological manifestation was first reported in 1920[3]. Type 2 Gaucher's disease, is an acute neuropathic form, has an incidence of 1:500000[2]. It presents during infancy with a neurological syndrome characterized by dysphagia, persistent head hyperextention, paralytic strabismus, trismus, generalized spasticity, myoclonic or generalized tonic-clonic seizure and psychomotor regression[2, 4]. Icthyosiform skin may provide a mean for early differentiation of type 2 and type 3 Gaucher's disease[5]. Death usually occurs by the age of 2 years as a result of progressive brainstem dysfunction[4].

Type 3 or subacute or chronic neuropathic form of Gaucher's disease has an incidence of 1:200,000[2]. It is phenotypically heterogeneous and had wide variation in age of presentation. Common childhood age of presentation is 4 years[6, 7, 8]. The features were also seen in our patient who also had his first symptoms starting at age 4 years. Four subtypes are distinguishable on clinical ground. 3A, 3B, 3C and Norbottnian variant. Type 3A present in children and young adult with seizure, gaze palsy, ataxia, spasticity and developmental regression[6, 7, 8]. Type 3B present in childhood and the children with aggressive systemic disease, gaze palsy and cognitive impairment leading to death in adolescence from the complication of portal and pulmonary hypertention[3, 6]. Type 3C has recently been described in Arab patients, in Israel and Spain in 1995[9]. They suffer from abnormal eye movement but no other neurological involvement, heart valve calcification and specific gene mutation (D409H) [9]. Norbottnian variant in Northern Spain present in childhood with aggressive systemic disease and slowly progressive heterogeneous neurological syndrome including horizontal supranuclear gaze palsy, dementia, spasticity, ataxia and myoclonic or complex partial seizures. They have single mutation L444P[9].

In NGD 20 different gene mutation has been identified. Lack of shared genotype and variability in clinical manifestation suggest that other modifications are also present[6, 9]. The most common mutation observed is L444P[6]. The second most common mutation is R463C[10]. The major clinical finding shared by all patients is horizontal saccadic eye movement irrespective of visceral involvement[12]. The Patterson at all suggests that occulomotor abnormality is predictor of several visceral involvement[6]. Gaucher cells are related to monocyte-histiocyte series. They are large and average 20 to 60 micm in cross-section with wrinkled cytoplasm. Abundant acid phosphatase activity is noted. The pathogenesis of neuronal dysfunction is a not known although most striking microscopic feature found in brain is the perivascular accumulation of gaucher cells in the Virchow-Robin spaces[2]. The diagnosis is made by decreased glucocerebrosidase activity in lymphocytes or fibroblast and molecular analysis of mutation allow for some prognostic action of disease severity and presence of foam cells on bone marrow examination helpful in establishing the diagnosis[13].

Figure 1 Gaucher cells (foamy Histiocytes) on the bone marrow examination.



Four forms of management have been described. Splenectomy has long been treatment of choice to avoid hypersplenism or to relieve pressure symptoms but still it had been matter of debate[13]. Now a day enzyme replacement therapy is a highly efficacious treatment for the hematological, visceral, and skeletal

manifestations of GD, this remains the first line of therapy[13]. It prolongs the lives of individual patient, but its use in type 3 is still contravertial[12, 14].The allogenic bone marrow transplantation improves the hematological and visceral manifestation but it has significant mortality and morbidity therefore it's limited in use[12]. The goal of gene therapy is to provide tissue with enzyme level allowing avoiding storage of undigested substrate [13, 15]. NGD is difficult to target by gene therapy because of no soluble nature of glucocerebrosidase[12, 13]. Studies of gene therapy in animal models of GD show promise, but this research is still preclinical[15].

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