Gaucher’s disease Type I

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Ceylon Medical Journal 2018; 63: 33-34
DOI: http://doi.org/10.4038/cmj.v63i1.8623

Introduction

Gaucher’s disease is an uncommon neurodegenerative lipid storage disease, caused by defective activity of lysosomal enzyme β-glucosidase/β-glucocerebrosidase. It is characterized by accumulation of glucocerebroside in the macrophage-monocytes system known as Gaucher’s cells [1]. It is an autosomal recessive disorder caused by pathogenic gene mutations of the GBA 1, encoding the enzyme β-glucosidase [2]. Generally, Gaucher’s disease is underdiagnosed due to its rarity and wide spectrum of clinical presentation. Based on the presence of CNS involvement, Gaucher’s disease is classified into three subtypes.

Case report

A 61-year-old retired bank officer was brought to hospital with a first episode of tonic-clonic seizures. He has been treated with antidepressants for five years. He was the child of non-consanguineous parents. He had developed symptoms of depression such as fatigue, reduced sleep, frequent irritability with outburst of severe anger and lack of interest in activities of daily living over the past 6 months. A consultant psychiatrist assessed him and diagnosed major depressive disorder. He has had intermittent symptoms of depression and persecutory delusions in the past.

Despite several medications prescribed for depression, the symptoms continued. His family members then noted other features such as memory loss, unsteady gait with frequent falls and binge eating.

On admission, he had a resting tremor and cogwheel rigidity suggestive of Parkinson’s disease, moderate hepatomegaly and mild splenomegaly. The mental state examination showed prominent features of depression along with some psychotic symptoms such as suspiciousness towards his wife and hearing voices of unknown persons. Cognitive assessment done using the Montreal Cognitive Assessment (MoCA) showed mild cognitive impairment.

Basic metabolic screening and routine investigations such as full blood count, blood picture, renal function, ESR, ECG, 2D echocardiography, non-contrast CT brain and EEG were normal except for moderately elevated liver enzymes. Serology for hepatitis B and C, serum ceruloplasmin, serum ferritin, ANA, ANCA (P and C) titer and ACE levels and 24 hour urine copper excretion were also normal. Serum level of β-Glucocerebrosidase was low (3.4 units; normal 4.8-8.9 units). Trephine bone marrow biopsy demonstrated large macrophages with eccentric nuclei and abundant granular and fibrillary cytoplasm consistent with Gaucher’s cells. The diagnosis of Gaucher’s disease was made in the presence of Parkinsonism, hepatospleno-megaly, low β-glucocerebrosidase and Gaucher’s cells in bone marrow. The patient was managed conservatively with a broad spectrum of anti-epileptic drugs and antidepressants.

Discussion

Gaucher’s disease can present in all age groups with a wide range features. The clinical features of Gaucher’s disease in adults generally appear before the age of 20 years. However, this spectrum of disorders is observed to be less severe or have a slower progression compared to those presenting during childhood [3]. Studies report that the incidence of Gaucher’s disease is 1:50000 even though the actual value is thought to be higher [3].

Organomegaly, bone disease causing skeletal abnormalities (including radiological abnormalities) or bone marrow involvement resulting in hematological abnormalities are common presentations of Gaucher’s disease type 1. Neurological manifestations, like Parkinsonism and fatal neurological consequences like hydrops fetalis, are

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less common. These manifestations are commoner in Type 2 and 3 [3]. Thus, Type 1 is differentiated from others based on the absence of neurological impairment, but in recent years few neurological manifestations particularly Parkinson’s disease and peripheral neuropathies have been reported. Ocular motor impairment, progressive myoclonic epilepsy, cerebellar ataxia, spasticity and dementia are well documented in juvenile subacute neurological Gaucher’s disease Type 3; whereas opisthotonus, bulbar palsy, trismus, psychomotor retardation and hypertonia are mostly reported in paediatric Gaucher’s disease Type 2 [4].

This patient had depression and persecutory delusions since the age of 30 years in addition to the current presentation of Parkinsonism, seizure disorders and visceromegaly. These symptoms raised the clinical suspicion of Gaucher’s disease which was confirmed by the reduced glucocerebrosidase activity in peripheral leucocytes. This phenotypic spectrum is more in favor of Gaucher’s disease Type 1.

The pathogenesis of different Parkinsonian phenotypes in Gaucher’s disease is possibly due to mutation of GBA1 related specific alleles. All related alleles comprising null alleles increase the risk of Parkinson’s disease. They are described both in neuropathic type gene mutation (especially1448T>C (L444P)) and non-neuropathy type gene (common) mutations related to N370S of GBA1 [6]. Due to non-availability of resources these genetic tests were not performed. These gene-mutations cause loss of function or decreased level of glucocerebrosidase resulting in slowdown of lysosomal α-synuclein degradation and accumulation of intracellular-glucocerebroside which further inhibits glucocerebrosidase activities or its production by blocking trafficking from the endoplasmic reticulum to the golgi leading to accumulation of α-synuclein containing cells and, later, form insoluble aggregates of Lewy bodies [4,5]. These toxic aggregates increase in the substantia nigra of the mid-brain resulting in symptoms of Parkinson’s disease and the fronto-temporal (Hippocampal) region resulting in progressive neuro-psychiatric symptoms. The onset and progression of these symptoms principally depend on the site where these substances are initially deposited [4].

Currently, there are two treatment options for Gaucher’s disease. These are enzyme replacement therapy and substrate reduction therapy. In enzyme replacement therapy, the enzyme is supplied to the lacking cells while in substrate reduction therapy the substrate is supplied to minimize the accumulation of toxic substances in the cells which initiate the cascade reaction. According to previous studies, osteopenia and bone marrow infiltration and bone pain regress with intravenous enzyme replacement therapy. However, none of the above treatments seems to improve the neurological symptoms of Gaucher’s disease [4].

**Conclusion**

Gaucher’s disease should be considered early in the differential diagnosis of patients with Parkinson’s disease despite the age at presentation if they have liver and spleen enlargement.

**Conflicts of interest**

There are no conflicts of interest.

**References**


