Genotype phenotype relationship in Gaucher's disease in Egypt

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Background: Gaucher's disease is the most prevalent of the genetic lysosomal storage disorders. It is an autosomal recessive disease which was described by French physician Philippe Gaucher in ١٨٨٢. It is caused by sever deficiency of glucocerebrosidase enzymatic activity with resultant accumulation of large quantities of glycolipid, glucocerebrosidase within the lysosomes of the phagocytic cells of the monocytes-macrophage system. Gaucher's disease is classified into three conventional types; type I: Chronic non-neuropathic form which usually found in adult especially in Jewish population, type II: infantile neuropathic form which always appears by ٦ month of age as a rapidly progressive neurological affection, and type III: Juvenile sub-acute neuropathic with slowly progressive neurological disease that begins during child-hood or adolescence. The aim of this study is to investigate the genotypes of Gaucher's disease, the most prevalent mutation in Egypt and to assess if a genotype-phenotype relationship could be elicited.

Patients and Methods: The present study included ٢٠ Gaucher's disease documented patients; they were ١٠ males and ١٠ females. Their ages ranged from ٣ to ٤٣ years with of a mean of ١٠.١٥ and median of ٦ years. All patients were subjected to clinical evaluation, revision of their filed clinical progress, radiological and laboratory data including full blood count, b-Glucocerebrosidase enzyme assay, liver enzymes, bone marrow and splenic aspirate. In addition, we studied the most common GBA mutations using strip assay which based on the reversed-hybridization principle. The assay covered ٨ of the most frequent GBA mutations: ٨٤GG (٤٥٢+G), IVS٢+١ (٤٨٤G>A), N٣٧٠S (١٢٢٦ A>G), V٣٩٤L (١٢٩٧ G>T), L٤٤٤P (١٤٤٨ T>C), R٤٩٦G (١٦٠٤ G>A) and ٢ recombinant alleles (RecNcil, Rec TL).

Results: Neither the age of patients, age of onset of the disease nor the sex showed significant relation with homozygosity Vs double heterozygosity or the different genotype groups. The most common mutations found in this study were L٤٤٤p/ L٤٤٤p (homozygous) and L٤٤٤p/IVS٢+١ (double heterozygous); ٨ patients each (٤٠%) followed by L٤٤٤p/D٤٠٩H (double heterozygous) in ٣ patients (١٥%) whereas N٣٧٠S/N٣٧٠S (homozygous) was the least common mutation found in only ١ patient (٥%).Allele frequency showed that L٤٤٤p was found in ٦٧.٥% of studied chromosomes, IVS٢+١ in ٢٠%, D٤٠٩H in ٧%, whereas N٣٧٠s was in only ٥%. As for family history, ٨٠% of cases had positive consanguinity; with ٤٥% of patient parents being first cousins. All homozygous cases showed positive consanguinity (٩ cases), where as only ٧ cases of ١١ of the double heterozygous showed positive consanguinity. Also all patients with the genotypes L٤٤٤p/ L٤٤٤p and N٣٧٠S/N٣٧٠S were from consanguineous parents; ٨ of٨ and ١of ١ respectively. On the other hand, the ٣ patients with genotype L٤٤٤p/D٤٠٩H had negative consanguinity, while the genotype L٤٤٤p/IVS٢+١ showed ٧ of ٨ cases with positive consanguinity and only ١ case with negative consanguinity.

Conclusion: The most common mutations found in our study were L٤٤٤p/ L٤٤٤p homozygous and L٤٤٤p/IVS٢+١ double heterozygous. L٤٤٤p was the most common allele. Analysis for the most common mutation was the method of choice for identification of Gaucher's disease carriers. Both age of the patients and onset of the disease had no significant relation with either homozygosity Vs. double heterozygosity or the different genotype groups. Gaucher's disease occurred with equal frequency in males and females. Patients with homozygous gene mutations tend to have consanguineous parents. Neurological manifestations, growth retardation and chest symptoms were the most common clinical conditions reported in studied cases. None of the previous conditions were significantly associated with certain genotype. No correlation was detected between genotype or homozygosity Vs heterozygosity on one side and either age of patients, age of onset or clinical manifestations on other side.

Keyword: GD (Gaucher's disease) – GBA mutations – Reversed hybridization – Homozygous – Double heterozygous.