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Genetic Analysis of Gaucher Disease in Pakistani Population and its Diagnostic Comparison

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Gaucher disease (GD) is most frequently observed in the Ashkenazi Jewish population, with an incidence in non-Ashkenazi populations ranging from about 1/40,000 to 1/60,000 births.[1] It is a rare lysosomal storage disease that is caused by the lack of enzyme β-Glucocerebrosidase which results in a buildup of uncatalyzed substrate glucocerebroside, glycosphingolipids, and glucosyl sphingosine in macrophages.[2] These macrophages lead to the formation of crinkled appearing cells, Gaucher cells. These pathognomic Gaucher cells infiltrate major organs like the liver, spleen, and bone marrow causing the complications of disease.[3] Clinical manifestations are mainly hepatosplenomegaly, anemia, thrombocytopenia, and bone problems. Based on the presence or absence of neurological involvement, the disease is divided into three subtypes: Type I, II & III. GD Type I is a non-neuropathic and present in almost 90% of the cases.[4]

Gaucher is a genetic disease that is inherited in an autosomal recessive pattern. *The GBA* gene responsible for the function of the deficient enzyme is mutated in this disease.[5] The GBA gene is positioned on the long arm of chromosome 1 (1q21). An almost 96% identical homologous pseudogene of GBA is also there, located 16 kb downstream of the functional gene.[6] The GBA gene comprises 11 exons and 10 introns and more than 250 variations have been reported. According to studies, exons 9 and 10 are hot spots of this disease in Asia and worldwide as the most common mutations like N370S and L444P are located in these exons.[7] Diagnostic strategies include bone marrow biopsy, enzyme assay, and genetic testing.[8] It can be difficult to differentiate Gaucher cells from pseudo-Gaucher cells present in other diseases which can lead to miss diagnosis of the patient. But being a third-world country and lack of awareness, around 60% of all new diagnosis is still made on bone marrow biopsy and not confirmed by enzymatic assay or detection of genetic defect. Genetic analysis of Pakistani patients with Gaucher disease that were diagnosed either on bone marrow or enzymatic assays showed distinctive results. Patients who were diagnosed with low enzyme levels were found to have L444P mutation which is most prevalent in our ethnicity. But the patients that were diagnosed on basis of bone marrow morphology did not exhibit any mutation on sequencing. This is an interesting discovery that underscores the importance of estimating enzyme levels in all cases suspected of Gaucher's disease (GD). This insight will establish a foundational framework for diagnosing and identifying patients with Gaucher's based on enzyme deficiency, thereby preventing overdiagnosis solely relying on bone marrow morphology.

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