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Dilemmas involved in diagnosis due to co-inheritance of 619bp deletion and HbD presenting as Hb D homozygous on hemoglobin electrophoresis screening

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Thalassemias are one of the most common single gene disorders present worldwide. Mutations in the globin genes are present in 7% of the worldwide population. These mutations can either affect the amount of the globin chain production and cause thalassemia or they can cause a change in the hemoglobin structure thus affecting the functions generating hemoglobin variants [1]. Hb S, Hb E,Hb D,Hb C are some of the common structural variants of hemoglobin and these result from single amino acid substitutions caused by point mutations.

Hb D-Punjab also known as Hb D-Los Angeles is one of the most commonly inherited structural hemoglobin variants with a high prevalence in the Punjab region in the North western part of India. It is caused due to a point mutation in the beta globin gene due to appoint mutation c.364G→C (rs33946267). Hb D can be inherited either in heterozygous or homozygous condition (which is the rarest form of inheritance) without causing any clinical symptoms [2]. Though its inheritance with thalassemias do not present any detectable symptoms but its inheritance with Hb S causing Hb S-D disease can cause clinical manifestations in patients with peculiar severity. According to the Globin Gene server database there are seven other types of Hb D reported so far caused due to different point mutations.

Around 200 mutations for thalassemia have been described so far and out of these some are found very commonly in some ethnic groups and populations [3]. Except for the 619 bp deletion mutation all the other common mutations are due point mutations, small insertion or deletion of few bases [1,4]. 619 bp deletion causes 20% of the beta thalassemias in Indian population [5].

The most common strategy that is followed in most of the diagnostic laboratories is to screen for the patients first by doing hemoglobin electrophoresis. Based on the results obtained and on the ethnic origin the next step is to proceed for mutation detection using ARMS to check for the most common mutations found in the population which can detect mutations in about 90% of the cases. If undetected then they are detected by sequencing the beta globin gene.

When there is a co inheritance of Hb D and 619 bp deletion it is seen as homozygous Hb D on hemoglobin electrophoresis. Though the presence of 619bp deletion can be seen as raised Hb A2 levels on Hb electrophoresis, many times they are not that high. This leads to misdiagnosis when the screening tests are not followed by confirmatory molecular analysis.

The 619bp deletion removes the 3' part of intron 2 and exon 3 but leaves the 5' part of the beta globin gene intact. That means the region where Hb D is usually present is also deleted. This may be the resulting in an Hb D homozygous pattern when an Hb D mutation is present on one chromosome and a 619bp deletion on the other chromosome.

Thus, one has to be extremely cautious while reporting such cases and molecular diagnosis has to be done for ruling out the presence of any other beta globin gene mutations present. If such a person (pseudo HbD homozygous) gets married to a thalassemia trait there is 25% chance of having a thalassemia major child. But if the patient is diagnosed as HbD homozygous based on Hb electrophoresis alone without molecular confirmation and since Hb D – beta thalassemia do not present the patient would never go for the screening of the partner or for a prenatal diagnosis and this would result in the birth of a thalassemia major child in the family.

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