Genotype Spectrum Among Children with Transfusion Dependent Beta-Thalassemia (TDT) at Woman and Children Hospital (WCH), Tunku Azizah Hospital (HTA), Malaysia

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The clinical severity of beta-thalassemia disease ranges from mild to severe clinical manifestations, including beta-thalassemia major that requires more than six transfusions per year and is classified as transfusion dependant thalassemia (TDT). The present study aims to determine genotype spectrum of TDT patients by evaluating the mutation of beta-globin gene with potential modifiers gene. Fifty-three TDT patients were genotyped, including homozygous or compound heterozygous beta-thalassemia and haemoglobin E (HbE) beta-thalassemia patients. Their clinical characteristics, and hematologic parameters were evaluated. Genotype analysis was performed using multiplex amplification refractory mutation system (MARMS), MGAP-PCR, and HBB gene sequencing. Co-inheritance with alpha thalassaemia was done using either GAP-PCR, ARMS-PCR and modifier genes, namely XMN-1 polymorphism and alpha triplication were assessed. From 53 TDT cases, majority of the patients are male, n= 28 (52.8%) with female n=25, (47.2%). Among the cases of beta thalassaemia major, majority were presented at age less than one year old (n = 25, 62.5%) with a mean age of 1.0 $\pm$ 2.8 years and 15 cases (37.5%) were presented at age older than one year old. As expected in the Hb E/ Beta thalassaemia group, majority of them presented later with a mean age of 3.4 $\pm$ 2.8 years (p-value < 0.0001). Most of them were Malay n = 38, (70.3%) followed by Chinese n = 10, (18.5%) and 1.0 + 2.8 others n = 5, (1.9%). We reported only one Indian case in TDT group. The most common beta-globin mutation was IVS 1-5 [G > C] found in 23 alleles (22.1%) followed by CD41/42 [-TTCT] in 17 alleles (16%) and IVS 2-654 [C > T] found in 8 alleles (7.5%). Interestingly few mutations that unexpectedly manifest as thalassaemia major in compound with other beta plus mutations were found namely CD19 [AAC > AGC], β+ Cap +1 5'UTR (A > C), Poly A [AATAAA > AACAAA] and Poly A [AATAAA>AATAGA] mutations. The said mutations are expected to have intermediate phenotype. Our finding revealed the correlation between genotype and phenotype of the beta-thalassemia major patients. This provides a better prediction of clinical manifestation and severity by early identification of the type of mutations.

Keywords: Beta-thalassemia, transfusion dependent thalasaemia (TDT), genotype spectrum

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