Multiple Cerebral Emboli in a Homozygous b-Thalassaemia Patient Due to Factor V 1299 (His-Arg) 4070 A-G Mutation

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ABSTRACT

Thromboembolic episodes are quite rare in beta thalassemia major patients although there is a tendency for thrombosis in haemolytic anaemias. We report a patient with cerebral thromboembolic episode triggered by a minor blood group incompatibility in which the underlying defect of factor V 1299 (His-Arg) was detected three years after his death.

Key Words: Thromboembolism, ß-thalassaemia, Factor V mutation.

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Central nervous system complications like convulsions, transient ischemic cerebral attacks, headaches, deafness, paresthesias, hyporeflexia, hemiplegia, and hemiparesia have been reported rarely in thalassaemia major[1-7]. These findings have been attributed to the release of vasopressins after multiple transfusions, leading to hypertension, encephalopathy and hemorrhaege[1,7] or to chronic anemia-hypoxia[3].

With a better knowledge of natural inhibitors of coagulation, it is now known that there is an increased tendency to thrombosis in haemolytic anemias, especially in thalassaemia major and sickle cell anemia. It has been reported by various investigators that deficiencies of protein C (PC), protein S (PS) and antithrombin III (AT III) have some role in this prothrombotic tendency[2,4,8]. Moreover, common genetic variant Factor V 1691 G-A mutation was found to increase the risk of thrombosis[9,10].

Recently, a genetic component in the Factor V gene that contributes to activated protein C (APC) resistance both in the presence and in the absence of FV 1691 G-A was reported[11-12]. This highly conserved FV gene haplotype was marked as R2 polymorphism, an A to G alteration at position 4070 in exon 13 that predicts the His 1299 Arg substitutions[13]. R2 haplotype was reported in po-

pulations including Somalis, Italians, Turks and Greek Cypriots[12-14].

Here we report a thalassaemic child who had convulsions, multiple cerebral thrombi and FV 1299 Arg-mutation which was detected three years after his death.

METHODS

Hemoglobin, hematocrit, and RBC levels were measured on the Coulter Counter, Model ZF; a hemoglobin electrophoresis was performed on the cellulose acetate at a pH 8.6 of molecular analyses. The antithrombin III (antigenic assay) was measured on a Turbitimer (Behring Institute) with AT III Turbitime System (Behring). Protein C levels (functional assay) were measured using a commercial clotting assay (Staclot Protein C, Diagnostica Stago) according to the manufacturer's instructions. A molecular analysis of the specific mutations FV 1691 G-A, PT 20210 G-A, and FV 4070 A-G was performed according to previously reported techniques[13,15,16].

CASE REPORT

The three-and-a half year old male patient was diagnosed with homozygous, b-thalassemia one year previously. On the first admission he was pale with a 4 cm hepatomegaly and 6 cm of splenomegly. Laboratory evaluations revealed a Hb of 8.6 g/dL, 29% Hct, 3.096.000. RBC/mm^3, 1% Rtc. On hemoglobin electrophoresis Hb A_2 was 1.5% and Hb F 86%. A molecular analysis revealed a compound heterozygosity for the mutation (FSC8/9/(+G) & IVS-IInt 1 G-A). His hemoglobin remained stable at about 8 g/dL for 6 months and no transfusions were required. Six months after his first admission, the patient had a focal convulsion which became generalized eventually. Neurological findings, EEG, and a brain CT were normal. Phenobarbital was begun and he was transfused because his hemoglobin had dropped to 5.4 g/dL.

Three weeks later he received his second transfusion and in a few hours developed a maculopapular rash, a 3 cm hepatomegaly, a 11 cm splenomegaly and hemoglobinuria. On the same day, right hemiparesis developed. Haptoglobin levels were below 20 mg/dL (normal range: 50-320 m/dL) Anuthrombin lll was 27 ng dL (Normal: 22-23 ng dL) the protein C (PC) level of the patient was 16% and those of his mother and father were 120 and 96%, respectively (Normal range 60-140%). Despite severe anemia (Hb 5.4 g/dL), no transfusions could be given immediately because anti-Kidd agglutinins (anti-Jk) were detected and he was transfused with a Jk negative blood. Despite the initiation of anticonvulsant, antiedema and anticoagulant therapy, he had frequent recurrent convulsions. Later in the course of the disease, a computerized brain tomography revealed multiple cerebral infarcts and edema. His follow-up PC level was found to be 80%.

The patient had spasticity and severe motor retardation; his last CT revealed ventricular dilatation, severe atrophic changes in the posterior fossa and in both cerebral hemispheres.

He died at the age of five. APC resistance could not be performed, as it was not available then. His DNA analysis for FV 1691 G-A and PT 20210 G-A was found negative for the specific mutations. FV 4070 A-G was found in the heterozygous state.

DISCUSSION

The first neurological complication described in thalassemia major was a clinical finding resembling Wilson's Disease, presumed to be due to degenerative changes in the striatum and pallidum as a result of hemosiderin deposition. Logothetis et al., Wasi et al., and Constantopoulos et al. reported various neurological complications in thalassaemic patients[1,3,7]. Sinniah et al. investigated coagulation factors in 60 thalassaemics and found cerebrovascular complications in 4 patients. They suggested that a prothrombinase inhibitor was responsible for these complication[5]. Musumeci et al. found deficiencies of PC in 70, and of AT III in 41 patients among 74 thalassemics. However, they have seen cerebrovascular accidents in only two[4]. Our patient had his first convulsion prior to any transfusions and later had hemiparesis and multiple cerebrovascular thromboembolic episodes. He was found to have a protein C deficiency, thongh his parents had normal levels. His follow-up PC level returned to normal. Therefore, we suggest that the PC deficiency was

not congenital and, because of his small age and lack of transfusions prior to his convulsions, was not due to hepatic dysfunction, either. While he was living, we postulated that the findings of the patient were due to three factors: namely, chronic hemolysis, intravascular hemolysis as a result of minor group incompatibility, and, finally, to an increased consumption of PC, together with the procoagulant proteins. Although the PC level had been normal at the beginning, it could have been consumed more rapidly in the event of a thrombus, and thus could have accelerated the thromboembolic episodes, as suggested by Jensen et al[2]. The detection of a normal PC level after the acute phase supported this hypothesis.

However, as an understanding of our knowledge has broadened during the last four years, we have had the chance to analyse his DNA for specific mutations, even thongh the patient had died. Factor V 1691 G-A and prothrombin 20210 G-A mutations were found negative. Recently when we analysed his DNA for the Factor V 4070 A-G mutation, we found it to be in the heterozygous state. As this particular mutation causes APC resistance[13,17], it is probable that FV 4070 G played a role in the pathogenesis of multiple cerebrla emboli in our patient.

More data is needed to determine the possible role of this mutation in CNS complications in children.

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