Fresh Frozen Plasma Plus Iron Therapy in Congenital Hypotransferrinemia in the Second Decade: A Dynamic Approach to Maintaining Hematological Stability

Konjenital Hipotransferinemide İkinci Dekatta Plazma ve Demir Tedavisi: Hematolojik Stabiliteyi Korumak için Dinamik Yaklaşım

Deniz Aslan

Gazi University Faculty of Medicine, Department of Pediatrics, Section of Hematology, Ankara, Turkey

To the Editor,

Congenital hypotransferrinemia (CH) is a rare disorder characterized by deficiencies in transferrin and consequently hepcidin in serum [1,2]. The former leads to anemia due to lack of transferrin-mediated iron delivery to erythroid cells, whereas the latter results in severe iron overload in all non-hematopoietic tissues. Fresh frozen plasma transfusions, as a natural source of transferrin, lead to hemoglobin (Hb) synthesis by increasing the iron supply to the marrow with a consequent increase in hepcidin production. Plasma is known to have no effect on iron overload [3].

In 2018, we reported the observational follow-up of a child affected by CH who had been successfully treated with monthly plasma transfusions fortified with oral iron since 2007 [4]. Our first-decade results showed both correction and stable control of Hb. Ferritin levels were also stabilized. However, at the start of the second decade, Hb and ferritin began to decline and the therapy was revised. We herein present the 44-month follow-up results with updated therapy of the original case for the conscious management of other cases.

By the second decade, with no change in patient compliance, a decrease in Hb and ferritin began, probably due to a growth-related increase of erythroid iron demand or a reciprocal interaction between the actors in iron metabolism (Figure 1). The two major factors affecting these levels in this therapy are transferrin (here, plasma transfusion) and iron (here, additional iron). Since monthly plasma transfusions were thought to provide sufficient transferrin for erythropoiesis and reducing the interval between transfusions would negatively affect quality of life, the change was made to the iron therapy. As the iron dose was at the upper limit (10 mg/kg/day elemental iron), its duration was extended from 7 to 10 days: for maximum iron-transferrin interaction time, iron was started 1 day prior to fresh frozen plasma transfusion and continued for 2 days beyond the 1-week administration (though fresh frozen plasma transferrin persists in the serum for 1 week considering its molecular half-life of 8-10 days [5]). Hb and ferritin were measured monthly. Serum iron was checked before and transferrin before and after transfusions. The physical and social development of the patient was also followed.

The 44-month follow-up revealed the following: a) the fall in Hb was controlled (Figure 1); b) the fall in ferritin was not completely controlled (Figure 1); c) growth and development remained stable (Figures 2A and 2B) and the patient's social skills were compatible with those of her peers while she successfully continued her education; d) no side effects were observed with either fresh frozen plasma or iron therapy. Average transferrin before and after transfusion was 39.3 mg/dL and 118 mg/dL, respectively. Average serum iron before transfusion was within normal limits (23.1 mg/dL).

This combination provides a sufficient and stable Hb level for normal growth and development. Despite mild fluctuations, the Hb level was maintained above 12 g/dL and no anemia or need for increased amounts of plasma transfused or frequency of transfusions developed, unlike in a previous case under plasma therapy alone [6]. In this case with relatively long-term follow-up, Hb decreased to a level of about 7.0 g/dL in 5 years and the frequency of transfusions was increased to every week for 2 months along with the amount of fresh frozen plasma transfused to maintain normal erythropoiesis until Hb normalized.

With plasma transfusions, iron storage declines. Additional iron can delay the development of ferritin decline but it cannot permanently prevent it. The explanation for this might be as follows: hepcidin is the key regulator of iron metabolism [7,8]. Although additional iron may increase hepcidin at first, the effect of active erythropoiesis augmented by additional

iron due to erythroferrone (ERFE) produced by erythroblasts is much stronger and reduces the hepcidin, facilitating prolonged ferritin stability [9]. After a constant return to normal sufficient erythropoiesis (in our patient, after the first decade), since ERFE is not required in this resting erythropoiesis phase and its hepcidin suppression disappears, an increase in hepcidin develops, leading to a reduction of iron, including toxic non-transferrin-bound iron [10], and a decline in iron storage (Figure 1).

Sufficient and stable levels of Hb can provide and support normal growth and development. The absence of iron overload in vital organs may also contribute to this physiological process.

Stable levels of erythropoietic indicators (e.g., Hb and reticulocytes) suggest that monthly fresh frozen plasma transfusion is sufficient for normal erythropoiesis. This report is the first to present fresh frozen plasma transferrin values in the pre- and post-transfusion periods, confirming this suggestion.

In conclusion, our experience of almost 14 years reveals that fresh frozen plasma plus iron therapy may be advantageous over standard fresh frozen plasma transfusion. With this therapy, the stable Hb control seen in this case in the first decade was re-achieved in the second decade. Despite a decline in iron storage, no anemia developed and there was no need to increase transfusion frequency. Optimal growth and development were achieved with minimal need for hospital services. Due to the reciprocal interactions between the actors of iron metabolism, a dynamic approach is necessary in the long-term treatment of CH to maintain hematological stability.

Acknowledgments

The author thanks the patient and her family for their willing participation in this study, Yekta Yakal for preparing the figures, and Corinne Logue Can for language editing.

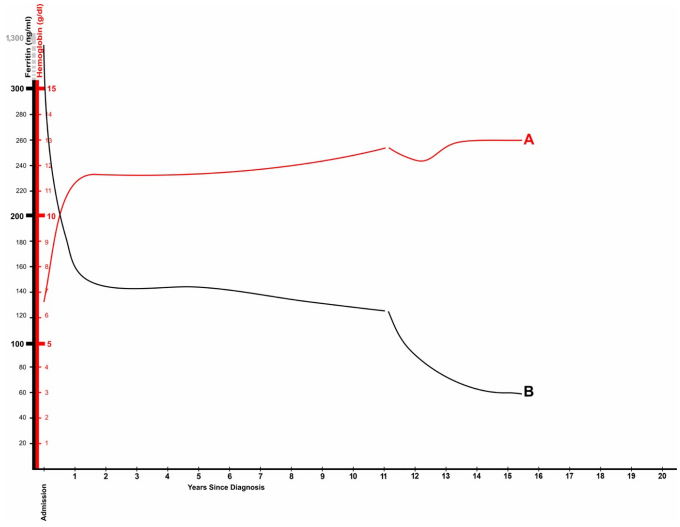

Figure 1. Hemoglobin and ferritin in the first and second decades.

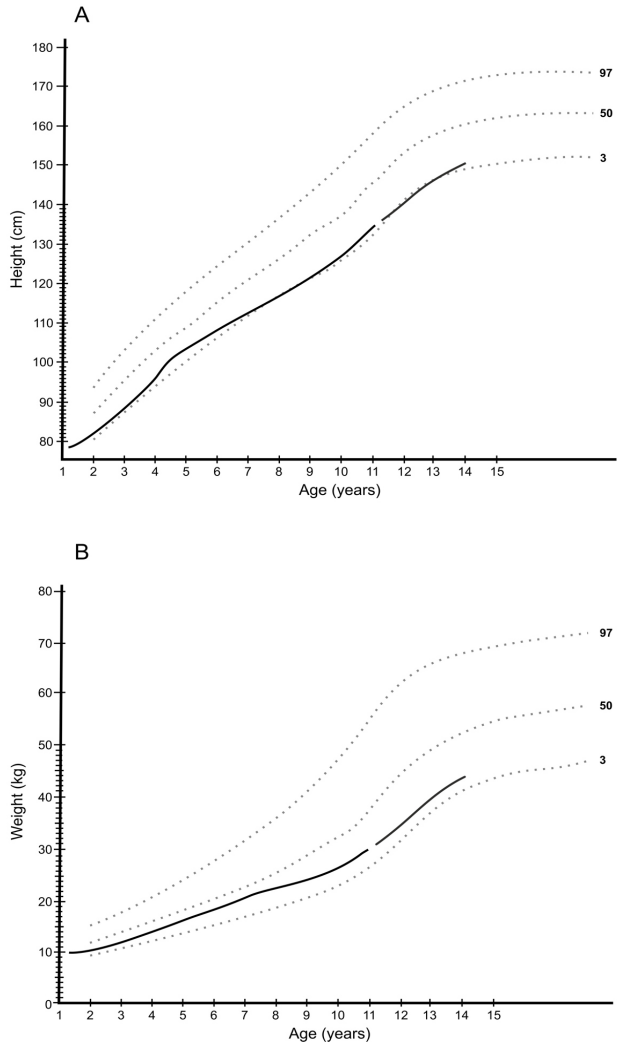

Figure 2. Growth and development remained stable (A, height; B, weight).

Keywords: Congenital hypotransferrinemia, Fresh frozen plasma plus iron therapy, Long-term follow-up, Dynamic approach in therapy

Anahtar Sözcükler: Konjenital hipotransferinemi, Taza donmuş plazma ve demir tedavisi, Uzun süreli izlem, Dinamik tedavi yaklaşımı

Financial Disclosure: The author declared that this study received no financial support.

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Address for Correspondence/Yazışma Adresi: Deniz Aslan, M.D., Gazi University Faculty of Medicine, Department of Pediatrics, Section of Hematology, Ankara, Turkey
E-mail : drdagutf@ttmail.com ORCID: orcid.org/0000-0002-5250-787X

Received/Geliş tarihi: October 20, 2021
Accepted/Kabul tarihi: November 17, 2021

DOI: 10.4274/tjh.galenos.2021.2021.0598

Immune-Mediated Thrombotic Thrombocytopenic Purpura after BNT162b2 Vaccine

BNT162b2 Aşısı Sonrası Gelişen İmmün Aracılı Trombotik Trombositopenik Purpura

Tekin Güney[1], Ferda Can[1], Sema Akıncı[1], Özge Soyer Kösemehmetoğlu[1], İmdat Dilek[2]

[1]University of Health Sciences Turkey, Ankara City Hospital, Clinic of Hematology, Ankara, Turkey
[2]Yıldırım Beyazıt University, Ankara City Hospital, Clinic of Hematology, Ankara, Turkey

To the Editor,

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare but life-threatening condition characterized by microvascular thrombosis [1]. The roles of several vaccines have been described in its etiology [2,3]. With the coronavirus disease-19 (COVID-19) pandemic, various vaccines have been developed. As a result of vaccine studies, the BNT162b2 (BioNTech) vaccine was approved by the US Food and Drug Administration in August 2021. The first case of iTTP following administration of BNT162b2 was reported around the same time [4].

A 48-year-old female patient was admitted to the hematology outpatient clinic on June 26 with complaints of weakness, nausea, dizziness, and bruising. There was no positive finding in her history, except that she had received the first dose of the BNT162b2 vaccine on June 14, 2021. She was taking no medications. She stated that ecchymoses had developed from the third day after vaccination. On admission, hemoglobin was 10.7 g/dL, platelet count was $88x10^9$/L, creatinine level was 0.5 mg/dL, lactate dehydrogenase (LDH) level was 515 U/L, reticulocyte count was $231x10^9$/L, Coombs tests were negative, and a peripheral smear showed polychromasia and normoblasts with schistocytes. Prothrombin and activated partial thromboplastin times were normal, the PLASMIC score was 6 with a high risk for ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency, and a polymerase chain reaction testing for SARS-CoV-2 was negative. ADAMTS13 enzyme activity was dramatically reduced to <0.2% with a high antibody titer level of >90 U/mL. Antiplatelet factor 4 testing cannot be performed in our center. As the patient was diagnosed with iTTP, methylprednisolone treatment at 1 mg/kg/day with one daily volume of therapeutic plasma exchange (TPE) was started. After 10 sessions of TPE, the patient had not responded (platelets $80x10^9$/L, LDH 368 U/L), and rituximab was added at 375 mg/m^2 once a week. After a total of 4 doses of rituximab, hemoglobin was 11.1 g/dL, thrombocyte count was $323x10^9$/L, and LDH was 472 U/L. ADAMTS13 activity was 0.2% with a persistently high antibody level of 50 U/mL one month after the last dose of rituximab. Additional immunosuppressive treatment was planned. Although COVID-19 vaccines have been in use for a limited period of time and there are still unknowns in the score calculation, the Naranjo Adverse Drug Reaction Probability Score was calculated as 6, meaning that the reaction was a probable adverse reaction.