



# Clinical characteristics of a Turkish family with congenital erythrocytosis due to an EPOR mutation: Is routine phlebotomy indicated in children and adolescents?

EPOR mutasyonuna bağlı konjenital eritrositozu olan Türk ailenin klinik özellikleri: Çocuk ve ergenlerde düzenli flebotomi gerekli midir?

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## The known about this topic

Erythropoietin receptor mutations (EPOR) cause primary congenital erythrocytosis (CE) with normal erythropoietin levels. CE may be inherited or sporadic. EPOR nonsense mutation c.1316G>A (p.Trp439Term) has been already identified in a few families. Headache, epistaxis, heat intolerance, nausea, vomiting, abdominal pain, tinnitus and vertigo are symptoms of erythrocytosis. Erythrocytosis may cause severe thrombohemorrhagic complications. Phlebotomy provides a transient relief in symptoms. Phlebotomy and low dose aspirin may prevent thromboembolic complications.

## Contribution of the study

Due to the rarity of CE, there are not many case reports presenting clinical course and outcome of the children and adolescents with this disease. Patients refuse phlebotomy during asymptomatic periods even if their hemoglobin is about 18 g/dL or more, and their compliance to aspirin treatment is not always satisfactory. Children, adolescents and young adults may not suffer from thromboembolic complications without any treatment. But in the same family, patients suffer from severe thrombotic attacks when they are older than 35 years. It may be suggested that in children and young adults with CE, routine phlebotomy is not indicated in asymptomatic periods but after 35 it may be recommended to prevent thrombotic attacks.

## Abstract

Here we present two siblings, a 9-year-old boy and a 15-year-old girl at presentation, with congenital erythrocytosis due to an EPOR c.1316G>A (p.Trp439Term) mutation. The patients had nausea, abdominal pain, and headache when they presented with hemoglobin levels of 23 g/dL and 19.4 g/dL, respectively. Their father, paternal uncle, and probably the paternal aunt and grandmother had congenital erythrocytosis. The siblings generally preferred to visit hospital when hyperviscosity symptoms developed and had intermittent phlebotomies. Their compliance to anti-aggregant and hematinic treatment was not satisfactory. Within the 11-year follow-up period, the siblings had no thrombohemorrhagic complications, whereas their 39-year-old uncle had a stroke. In addition to antiaggregant treatment, phlebotomy during hyperviscosity symptoms may be safe in children and adolescents; routine phlebotomies may be recommended to adults to prevent thrombohemorrhagic complications.

**Keywords:** Adolescent, children, congenital erythrocytosis, EPOR mutation

## Öz

Bu yazıda başvuru sırasında 9 yaşında erkek ve 15 yaşında kız olan, EPOR c.1316G>A (p.Trp439Term) mutasyonu nedeniyle konjenital eritrositoz tanısı alan iki kardeş sunulmuştur. Hastalar bulantı, kusma, karın ağrısı ve baş ağrısı yakınmaları ile başvurduklarında hemoglobin değerleri sırasıyla 23 g/dL ve 19,4 g/dL bulunmuştur. Babada, amcada ve muhtemelen hala ve babaannede de konjenital eritrositoz vardı. Kardeşler genellikle hastaneye hiperviskozite belirtileri olduğunda başvurmayı tercih ettiler ve aralıklı flebotomiler yapıldı. Antiagregan ve hematinik ilaçlara uyumları da iyi değildi. On bir yıllık izlem sürecinde kardeşlerin tromboz-kanama ardsorunları olmazken, 39 yaşında amcada inme gelişti. Anti-agregan tedavinin yanısıra hiperviskozite belirtileri olduğunda flebotomi yapılması çocuklarda ve ergenlerde güvenli olabilirken, erişkinlere tromboz-kanama ardsorunlarını önlemek için düzenli flebotomiler önerilebilir.

**Anahtar sözcükler:** Çocuk, EPOR mutasyonu, ergen, konjenital eritrositoz

**Cite this article as:** Sarper N, Zengin E, Gelen SA. Clinical characteristics of a Turkish family with congenital erythrocytosis due to an EPOR mutation: Is routine phlebotomy indicated in children and adolescents? Turk Pediatri Ars 2020; 55(3): 312–5.

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**Received/Geliş Tarihi:** 31.07.2018 **Accepted/Kabul Tarihi:** 22.01.2019

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DOI: 10.14744/TurkPediatriArs.2019.65481

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## Introduction

Congenital erythrocytosis (CE) is a group of rare disease and has primary and secondary forms owing to serum erythropoietin (EPO) levels. In patients with high oxygen affinity hemoglobin (Hb) variants, 2,3-bisphosphoglycerate deficiency, methemoglobinemia or having mutations in the genes involved in the hypoxia sensing pathway (VHL, EPAS1, and EGLN1), serum EPO is higher than normal subjects due to tissue hypoxia. In contrast, mutations in the EPO receptor (EPOR) produce hypersensitivity to EPO stimulus, the defect is intrinsic to the red blood cell progenitors, serum EPO concentration is not high, and it is classified as primary CE. Congenital erythrocytosis can be inherited either in an autosomal dominant or recessive mode, with sporadic cases arising *de novo* (1, 2). Until 2016, 116 individuals from 24 families were reported with primary CE due to EPOR mutations (3). All known mutations were located in exon 8, which encodes the C-terminal negative domain of the protein. In a study of 70 unrelated patients with erythrocytosis, EPOR mutations were detected in only five patients. Some of these five adult males required regular phlebotomies and hemoglobin levels were between 18.2–19.3 g/dL (2). Some novel EPOR mutations were reported in 2018 (4). There are still many patients with CE in whom molecular defects have not been defined. Here, we report the clinical characteristics of two siblings with EPOR mutations with intermittent hyperviscosity symptoms.

## Case

**Case 1** – A nine-year-old boy presented with a 4-day history of nausea, vomiting, and mild abdominal pain. He was referred to the hematology department due to elevated hemoglobin (Hb) levels. The patient's medical history was unremarkable. The mother reported that the boy's paternal uncle had heat intolerance and erythrocytosis. There was a 12-year-old sister. They reported that the parents and sister were healthy. Performing blood counts of the parents and sister was requested but they refused.

Physical examination was normal except plethora. Vital functions were normal. His height was 130 cm (50<sup>th</sup> percentile), body weight 26.5 kg (25–50 percentile). Peripheral capillary oxygen saturation was 95%, and there was no history of pulmonary and heart disease.

Blood counts were Hb 23 g/dL, hematocrit (Hct) 66.9%, red blood cell 8.85 million/mcL, leucocyte 9.520/mcL, mean corpuscular volume (MCV) 75.6 fL, RDW 20.3, thrombocyte 199.100/mcL. Blood biochemistry including serum lipids were normal. In a four-day period, four phlebotomies each 175–200 mL were performed and

equal volume intravenous crystalloids were infused. Hemoglobin decreased to 15.1 g/dL. The serum EPO level was 4.1 mU/mL (normal 5.9–16.7). Hemoglobin (Hb) electrophoresis performed with high-performance liquid chromatography (HPLC) detected no abnormality (HbA 83%, HbA2 2.3%, HbF 0%). Analysis of JAK2 and BCR/ABL revealed no mutation. Ferritin was 4.43 ng/mL. Oral ferrous-sulfate and acetylsalicylic acid 100 mg/day was started. During follow-up, phlebotomies were performed every three to four months when Hb was higher than 18 g/dL. Probably due to the pain of venesection, the boy said that he was well and phlebotomy made no difference. Three years later they reported that the uncle with erythrocytosis had a stroke at the age of 39 years. He was a smoker. He then started routine phlebotomies and paraparesis subsided.

After age 11 years, his Hb was about 17 g/dL for two years (only 5 visits) and he was asymptomatic and no phlebotomies were performed. At the age of 16 years, he presented with headache and nausea and with a Hb of 21.8 g/dL. Phlebotomy (500 mL) was performed. At the age of 17 years, he reported that he had not using acetylsalicylic acid for three years. He is now aged 20 years and visits the center for phlebotomy about once a year.

**Case 2** – Three years after the presentation of the first patient, an elder sibling, a 15-year-old adolescent girl presented with vertigo, nausea, and plethora. The physical examination was normal except plethora. Vital functions were normal and peripheral capillary oxygen saturation was 95%. Her height was 161 cm, and body weight 53.5 kg. Blood counts were Hb 19.4 g/dL, Hct 64.6%, MCV 87fL, leucocyte 6.500/mcL, absolute neutrophil count 4010/mcL, thrombocyte 168 000/mcL. The serum EPO level was 6.44 mU/mL, serum ferritin level was 4.1 mU/mL, and Hb electrophoresis using HPLC showed no abnormality (HbA 83%, HbA2 2.3%, HbF 0). Analysis of JAK2 and BCR/ABL revealed no mutation. Phlebotomy (450 mL) was performed, acetylsalicylic acid 100 mg/day and oral ferro-sulfate was started. In the following year, she presented with similar symptoms twice and two more phlebotomies were performed. Her Hb was between 20.4–18.4 g/dL when she had some symptoms. She is aged 23 years now and says that her plethora increases after a bath but she is well and she refused phlebotomy in recent years.

The patients reported that their father was aged 45 years and had tinnitus and erythrocytosis. The grandmother died of stroke at the age of 52 years. The paternal aunt also died at the age of 52 years. It is not clear whether the grandmother and aunt also had erythrocytosis.

Written consents of the patients were obtained for the genetic study, which revealed that the siblings were both heterozygous for the EPOR nonsense mutation c.1316G>A (p.Trp439Term).

### Discussion

The term erythrocytosis must be preferred instead of polycythemia in congenital (inherited) forms to distinguish it from polycythemia vera. Primary erythrocytosis is characterized by physiologic or low serum EPO levels, whereas secondary erythrocytosis with high EPO levels is due to factors extrinsic to the erythroid compartment, such as hypoxia due to living in high altitude, lung disease, cyanotic congenital cardiac disease or EPO-secreting tumor. The acquired form of primary erythrocytosis is polycythemia vera due to a somatic mutation in JAK2 V617F and JAK2 exon 12 mutations. It is easy to differentiate CE from this clonal myeloproliferative form where increased leucocytes, thrombocytes, and commonly splenomegaly are characteristic findings (5). There was only increased erythrocyte mass in our siblings with a history of affected paternal relatives.

Twenty-three germline mutations in exon 8 of EPOR have been described and registered in the website <http://www.erythrocytosis.org> (5). The mutation identified in this family was already reported by De la Chapella et al. (6) and Percy et al. (7). De la Chapella et al. described a Finnish family and performed genetic studies in 29 affected family members. The Hb range was 18.3–23.1 g/dL in males and 17.7–20.0 g/dL in females. They reported that lifespan was unaffected and one of the affected family members was a cross-country skier and won three Olympic gold medals and two world championships. Percy et al. (7) described a *de novo* mutation in a 16-year-old English boy with Hb 20.5 g/dL who presented with epistaxis, headaches, and heat intolerance. Erythrocytosis was defined as an elevation in Hb and hematocrit (Hct) levels (Hb>16 g/dL, Hct >48% in women or Hb >16.5 g/dL, Hct >49% in men). For children, it is defined as Hb and Hct values in at least two separate blood counts performed at different time points, and if relative erythrocytosis is excluded or at least unlikely, values >99<sup>th</sup> age-adjusted percentile or hemoglobin increase >2 g/dL from baseline (8). The main goal of therapy in CE is to prevent thrombohemorrhagic complications (9), but the risk of thrombosis is not clear in children and adolescents with CE.

The presented siblings who are now aged 20 and 23 years, they generally preferred to visit hospital when they had hyperviscosity symptoms and intermittent phlebotomies were performed. During growth spurts in the adolescent boy, Hb levels were lower probably due to the rapid in-

crease in the body mass. The occurrence of spontaneous remission of erythrocytosis after premature puberty and menstrual bleeding in a 10-year-old girl with a novel EPOR mutation was reported (4). In the present study, it seems that family members were affected by a dominant germline mutation. They had plethora and sometimes had headache, vertigo, tinnitus, nausea, vomiting, heat intolerance, and mild abdominal pain. The paternal uncle had a stroke at the age of 39 years and grandmother died of stroke at the age of 52 years. The paternal aunt also died at the age of 52 years but her medical data were not clear. We are not aware of comorbid factors, but probably erythrocytosis caused cerebral vascular occlusions. In a report from a family with an EPOR mutation, a 37-year-old man had angina and stent implantation. There was also a cardio bypass operation in a 65-year-old male member of the family (4). Fatal complications of intracerebral hemorrhage, deep vein thrombosis (DVT), coronary disease, and myocardial infarction are reported generally in adult patients, but DVT and hypertension are reported in 18 and 20-year-old adolescents, respectively. Good hydration, avoiding smoking, mountain climbing, and scuba diving are recommended. Taking precautions for long-distance airline flights is also important (1).

A new mutation in EGLN1 (PHD2 gene) has been detected in two generations of a Portuguese family with secondary CE. The proband had a Hb of 18.2 g/dL and Hct of 58% for at least 5 years. There was intermittent headache and hypertension. The age of the patient was not reported but there were no thrombotic events. The authors suggested that more studies were required to better understand genotype-phenotype correlations (10). In our Turkish family with the EPOR mutation, the highest Hb was 23 g/dL in the male sibling and 20.4 g/dL in the female sibling.

In the diagnostic approach to a child with erythrocytosis, family history (stroke, myocardial infarction, bleeding) and screening family members with full blood counts, physical examination of pulmonary and cardiovascular systems, oxygen saturation, serum EPO level, and hemoglobin electrophoresis are essential before mutation analysis.

The present patients reported no symptoms when Hb was ≤18 g/dL. Evidence is lacking to define the best management. It is not clear whether Hb levels alone or hyperviscosity symptoms are the indication for phlebotomy in children. Acetylsalicylic acid and iron support should be prescribed at all ages. Routine phlebotomies seem more important in patients older than 35 years because arterial thrombotic complications of the vital organs were generally reported in these patients.

There is no conflict of interest of any author. Consent of the patients for publication was obtained.

**Acknowledgement:** Thanks to Oliveira AC and Bento C from Hematology Department, Coimbra University Portugal for genetic study.

**Informed Consent:** Informed consents of patients were obtained for publication of case reports.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - N.S.; Design - N.S.; Supervision - N.S., E.Z.; Materials - N.S., E.Z., S.A.G.; Data Collection and/or Processing - N.S., E.Z., S.A.G.; Analysis and/or Interpretation - N.S.; Literature Review - N.S.; Writing - N.S.; Critical Review - E.Z., S.A.G.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Teşekkür:** Genetik çalışma için Coimbra Üniversitesi, Portekiz'den Oliveira AC ve Bento C'ye teşekkür ederiz.

**Hasta Onamı:** Genetik çalışma ve hasta bilgilerinin yayınlanması için onam alındı.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Yazar Katkıları:** Fikir - N.S.; Tasarım - N.S.; Denetleme - N.S., E.Z.; Malzemeler - N.S., E.Z., S.A.G.; Veri Toplanması ve/veya İşlemesi - N.S., E.Z., S.A.G.; Analiz ve/veya Yorum - N.S.; Literatür Taraması - N.S.; Yazıyı Yazan - N.S.; Eleştirel İnceleme - E.Z., S.A.G.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Mali Destek:** Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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