Neonatal Polycythemia May be Free of *JAK2V617F* Mutation

Yenidoğan Polisitemisi *JAK2V617F* Mutasyonundan Bağımsız Olabilir

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ABSTRACT Objective: Polycythemia is known as increased erythrocytosis and is linked to the erythropoiesis cascade including erythropoietin, erythropoietin receptor and intracellular signaling proteins. The Janus kinase 2 (JAK2) is the key signal transducer in the erythropoiesis cascade. A function gain mutation *(V617F)* at JAK2 gene has been identified in polycythemia vera in adults. On the other hand, the molecular etiology of neonatal polycythemia has not been elucidated well. Thus, the aim of this randomized controlled study was to investigate the role of *JAK2 V617F* mutation in the etiology of neonatal polycythemia similar to polycythemia vera. **Material and Methods:** Fifty-one neonates diagnosed with polycythemia according to venous hematocrit level over 65% and 26 healthy neonates as the control group were enrolled in the study in addition to 43 adult patients diagnosed with polycythemia vera. *JAK2 V617F* mutation analysis was performed using Real-Time PCR system. **Results:** All the neonatal polycythemia patients were negative for the specific mutation *JAK2 V617F*, as well as 26 control neonates, whereas in 31 (72%) out of 43 adult polycythemia vera patients, *JAK2 V617F* mutation was present. **Conclusion:** This is the first report showing that *JAK2-V617F* mutation may be an acquired somatic mutation instead of congenital and neonatal polycythemia is not related to the disrupted erythropoiesis cascade.

Key Words: Polycythemia; polycythemia vera; janus kinase 2; infant, newborn; mutation

ÖZET Amaç: Polisitemi artmış eritrositoz olarak bilinmektedir ve eritropoetin, eritropoetin reseptörü ve hücre içi sinyal proteinlerini kapsayan eritropoez zinciri ile bağlantılıdır. Janus kinaz 2 (JAK2), eritropoez zincirindeki anahtar sinyal iletim proteini olup, eritropoezin tek hücre içi kinaz proteinidir. Erişkinlerde görülen polisitemi vera hastalığının moleküler zemininde *JAK2* geninde bir fonksiyon kazanım mutasyonu olan *v617f* tanımlanmıştır. Diğer taraftan, yenidoğan polisitemisinin moleküler etiyolojisi çok iyi aydınlatılamamıştır. Bu randomize kontrollü çalışmanın amacı, polisitemi verada olduğu gibi Janus Kinaz 2 (JAK2) V617F mutasyonunun yenidoğan polisitemisinin de etyolojisinde etken olup olmadığını araştırmaktır. **Gereç ve Yöntemler:** Venöz hematokrit düzeyi %65'in üzerinde olmasına göre polisitemi tanısı konulan 51 yenidoğan hasta ile kontrol grubu olarak 26 sağlıklı yenidoğan çocuk çalışılmıştır. Ek olarak, polisitemi vera tanısı almış 43 erişkin hasta çalışmaya dahil edilmiştir. *JAK2 V617F* mutasyon analizi gerçek zamanlı polimeraz zincir reaksiyonu yöntemi ile yapılmıştır. **Bulgular:** Yenidoğan polisitemisi olan 51 hasta, kontrol grubundaki 26 yenidoğana benzer şekilde, özgül *JAK2 V617F* mutasyonu açısından negatif bulundu. Ancak, 43 erişkin polisitemi vera hastasından 31 (%72)'inde *JAK2 V617F* mutasyonu tespit edildi. **Sonuç:** Bu çalışma ile literatürde ilk kez *JAK2 V617F* mutasyonunun konjenital olmak yerine, sonradan kazılan bir somatik mutasyon olabileceğini gösterdik. Böylece, yenidoğan döneminde görülen polisiteminin bozulmuş eritropoez kaskadı ile ilişkili olmadığını bildirdik.

Anahtar Kelimeler: Polistemi; polistemia vera; janus kinaz 2; bebek, yenidoğan; mutasyon

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Neonatal polycythemia (NP) is known as increased red blood cell (RBC) mass with a venous hematocrit level (Htc) ≥65% of the norm that leads to hyperviscosity of the blood.[1,2] The incidence of polycythemia and hyperviscosity in term newborns has been reported as 1-2% among all live births up to 12% with an increase from sea level to higher altitudes.[3-5] Although the disorder is thought to be physiologic and is allied with transient and likely reversible symptoms such as tachypnea, lethargy, poor feeding, hypoglycemia, jitteriness, and cyanosis, if not diagnosed and treated efficiently, it sometimes may cause life threatening insults to neonates through cerebrovascular events with permanent damage, necrotizing enterocolitis and developmental impairment.[5-7]

Chronic fetal hypoxia, acute fetal hypoxia, delayed cord clamping and stripping of the umbilical cord are suggested to be common underlying mechanisms of neonatal polycythemia.[4,5] In each case, basic pathophysiology of erythropoiesis might be triggered because of decreased oxygen delivery to the kidneys. Hence, increase in fetal erythropoiesis, RBC mass, hematocrit and blood viscosity could be observed in response to increased erythropoietin (EPO) production. Circulating erythropoietin is able to respond effectively to changes in tissue oxygen tension and stimulates the production of RBCs as the master regulator of erythropoiesis to overcome the hypoxia.[5,8]

The Janus kinase-2 (JAK2) protein is a cytoplasmic tyrosine kinase. It is expressed widely and accomplishes a central role in transduction of signals coming from multiple growth-factor receptors.[9] Since erythropoiesis is tightly regulated by a cascade of signaling, the process starts by initial binding of EPO to its receptor (EPOR), thereby activating its unique cytoplasmic kinase JAK2 (Janus Kinase 2). Jak2 then activates signal transductor and transcription activator 5 (STAT5).[10] STAT5 finally migrates to the nucleus and activates crucial genes for proliferation, differentiation, and survival of erythroid progenitors.[11] Recently, an activating mutation (V617F) in the pseudokinase domain of Jak2 has been described by five unrelated research teams and was found to be associated with myeloproliferative diseases comprising polycythemia vera (PV), essential thrombocythemia and chronic idiopathic myelofibrosis in adults.[11-15] Hyperactivation of JAK2 due to a mutation, valine-to-phenylalanine substitution at amino acid position 617, is associated with over 90% of polycythemia vera cases and contributes to massive hematopoiesis by increasing hypersensitivity to EPO and other cytokines through constitutive tyrosine phosphorylation activity.[12,16,17]

Considering that JAK2 is a key protein in the signaling cascade of erythropoiesis, in this study we aimed to identify whether there is an activating mutation (V617F) of the JAK2 protein in the etiology of neonatal polycythemia, as well as polycythaemia vera.

MATERIAL AND METHODS

This study was conducted in the Trabzon Woman's and Children Hospital, and the Hematology Unit of Trabzon Numune Training and Research Hospital from January 2011 to September 2011. The Local Ethical Committee of the Trabzon Numune Training and Research Hospital approved the study protocol. Blood samples and genomic DNA was collected form the participants with informed consent in agreement with the World Medical Association (WMA) Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects 2008.

NEONATAL GROUP

According to the routine screening program for neonatal polycythemia, any infant with suggestive clinical features of polycythemia were examined for the diagnosis of polycythemia.[18] A venous blood sample of neonates' has driven for spun Hematocrit (Htc) if their heel stick Htc level obtained at 4th to 6th hr postpartum was exceeding 70%, and venous Htc levels over 65% were diagnosed as polycythemia. Fifty-one neonates diagnosed with polycythemia and treated with partial exchange transfusion (PET) and 26 healthy neonates were enrolled in the study. The indication for PET accord-

ing to the current standard neonatal practice was a symptomatic newborn with an Htc level ≥65% or an asymptomatic newborn with an Htc level ≥70%. Blood samples for JAK2 mutation analyses were collected during the PET procedure. The demographic features (birth weight, gestational age, type of delivery, gender, maternal age, and maternal diseases) were listed in Table 1. Blood samples were collected from a peripheral vein into three ml EDTA containing tubes and to heparinized microcapillaries (110 mm length and 1-2 mm internal diameter) at 4-6 hr following birth to obtain hematological data [white blood cell (WBC), Htc, platelet (PLT)] and to measure the venous Htc level, respectively.

ADULT GROUP

Forty-three patients who were diagnosed with polycythemia vera according to the World Health Organization (WHO) criteria and referred to Trabzon Woman's and Children Hospital, Genetic Diseases Diagnosis Center for JAK2 V617F mutation were included to study.[19,20] The mean age was 62.4± 15.0 [mean±standard deviation (SD)] year. The demographic and clinical features of the participnats were shown in Table 2. Nine cases (21%) developed thrombo-ischemic event such as acute myocardial infarction, deep venous thrombosis, pulmonary venous thrombosis or cerebrovascular event. Three ml EDTA-blood was collected from peripheral blood for mutation analyses.

BLOOD COUNT

WBC and PLT were measured vith automated blood analysis unit (Shenzhen Mindray, BC-5800 Auto Hematology analyzer, Germany). Since, spun Htc values were known to be higher than values obtained by the Coulter counter method and to show a better correlation with viscosity the Htc values were measured using centrifugation (ELEKTROMAG M19, Turkey) of capillary tubes at 10 000 rounds per minute for 3-5 minutes.[21,22]

DNA EXTRACTION AND JAK2 V617F MUTATION ANALYSES

DNA was extracted using MagNA Pure Compact Nucleic Acid Isolation Kit I (Roche, Penzberg, Germany) according to the manufacturer's instructions *(www.instructions.roche.com).* Genotyping was performed using a 7500 Real-Time PCR system (96-well format) (Applied Biosystem, Foster City, CA, USA) using a primer probe set of the JAK2 V617F system (Dr. Zeydanli Life Sciences, Ankara, Turkey) including the Taqman probe and having 5′-3′ exonuclease activity. PCR reaction was set according to the manufacturer's

TABLE 1: Demographic characteristics of the neonatal group.

	NP group (n=51)	Control group (n=26)	p values
Demographic characteristics			
Sex (M/F)	27/24	16/10	0.472
Gestational age (week) (mean±SD)	37.1±2.9	39.2±1.0	0.001
Birth weight (g) (mean±SD)	2783.3 ± 957.1	3546.9±400.2	0.001
Cesarean delivery	31 (60.8%)	8 (30.8%)	0.013
Maternal age (years) (mean±SD)	30.2±4.6	21.7±2.5	0.005
Clinical Symptoms			
Maternal diabetes	1 (2%)	1 (4%)	0.628
Preeclampsia at pregnancy	3 (6%)	0 (0%)	0.212
Tachypnea	17 (33%)	0 (0%)	0.001
Feeding intolerance	23 (45%)	0 (0%)	0.001
Hypoglycemia	0 (0%)	0 (0%)	0.001
Necrotizing enterocolitis	1 (2%)	0 (0%)	0.479

F: female; M: Male; NP: Neonatal polycythaemia; SD: Standard deviation.

TABLE 2: Demographic characteristic of the polycythemia vera group.

	PV group (n=43)
Demographic characteristics	
Sex (Male/Female)	23 (53%) / 20 (47%)
Age (years) (mean±SD)	62.4 ± 15.0
Clinical Symptoms	
Thrombo-ischemic event	9 (21%)

PV: Polycythemia vera; SD: Standard deviation.

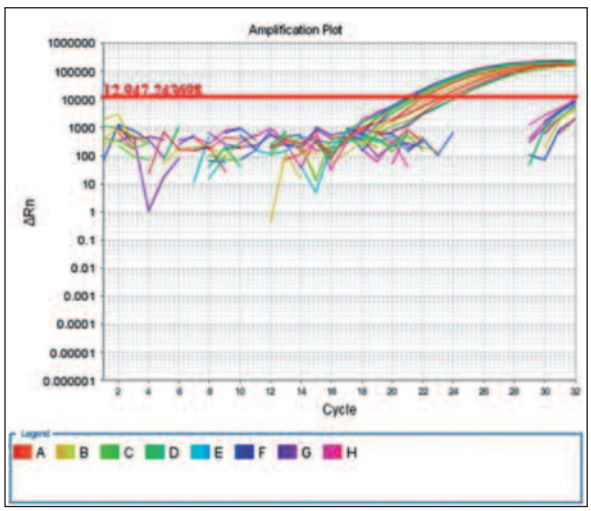

FIGURE 1: Real time polymerase chain reaction (PCR) amplification plot graphic of JAK2 V617F mutation. (ABI PRISM 7500, Applied Biosystem, Foster City, CA, USA). X-axis on the graphic showing PCR cycles and Y-axis showing a logarithmic indication of intensity of the emitted light from the dye in the excited state. ΔRn is an increment of fluorescent signal at each time and cycle point. Fractional PCR cycle number (Ct) for each sample is defined according to Treshold level (horizontal line). Ct values around 23 were considered positive whereas Ct values around 31 were negative.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

instructions. Basicly, the reactions were started with 95°C for 10 minutes, and 32 cycles of 95°C for 15 seconds and 60°C for 1 minute. Analyses were done using the intensity of the emitted light from the dye and Fractional PCR cycle number (Ct) defined according to the adjusted Treshold level (Figure 1).

STATISTICAL ANALYSES

Statistical analyses were done only within the neonatal group. Data were analyzed by using Statistical Package for the Social Sciences (SPSS) 11.5 for Windows (Chicago, Illinois). Differences between neonatal groups were analyzed with χ^2 and Student's *t* tests. A p value <0.05 was considered statistically significant.

RESULTS

All neonatal polycythemia patients and 26 control neonates were negative for the specific mutation JAK2 V617F (Table 3) (Figure 1), whereas in 31 (72%) out of 43 adult polycythemia vera patients *JAK2 V617F* mutation was present. Demographic characteristics and clinical features of the Neonatal group and the Polycythemia vera group were given in Table1 and Table 2.

DISCUSSION

In this study, we addressed the question whether a recently identified unique *JAK2 V617F* mutation could also give rise to neonatal polycythaemia besides Polycythaemia Vera. Due to lack of mutation in any of the neonates, we compared the results with polycythemia vera patients and did not extend the study to healthy adults.

Polycythemia vera pertain to myeloproliferative neoplasms and is primarily characterized by erythrocytosis that harbors the JAK2 mutation in almost all patients.[11] Basically, the mutation occurs in the pseudokinase domain of an enzyme-JAK2- that kidnaps the active part of the enzyme from negative regulation conferring hypersensitivity to, or independence from erythropoietin, resulting in abnormal proliferation and survival of affected erythropoietic stem cells.[23] When polycythemia vera is suspected, the presence of a JAK2 mutation confirms the diagnosis. The prevalence of the JAK2V617F mutation has been reported as 82% (between 65% to 95%) over 1000 polycythemia vera patients and 85.7% in the Turkish PV population by Kozan et al.[24,25] Consistent with the literature, we found *Val617Phe JAK2* mutation in 72% of our Polycythaemia Vera suspected patients whereas the neonatal polycythaemia group lacked the mutation.

Discovery of an activating tyrosine kinase mutation -the so called- JAK2 V617F in polycythemia

TABLE 3: Hematological parameters and *JAK2V617F* mutation in the neonatal polycytemia, control and plycytemia vera group

	Neonatal Patients			
	NP	Control		Polycythaemia Vera
	(n=51)	(n = 26)	p values	(n = 43)
WBC (x10^3/μL) (mean ± SD)	17.9±7.1	14.5±6.0	0.04	11.7±4.3
Hematocrit (%) (mean±SD)	70.1±2.9	48.8±5.9	0.001	49.7±5.2
Thrombocyte (x10^3/μL) (mean±SD)	168.6±62.6	280.5±109.2	0.001	419.8±264.3
JAK2V617F mutation (%)	None (0 %)	None (0 %)	-	31 (72%)

NP: Neonatal polycythaemia; PV: Polycythaemia vera; SD: Standard deviation; WBC: White blood count.

vera, has generated a great deal of interest in the JAK2 mutation. The Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway is one of the main signaling pathways that control eukaryotic cell proliferation, differentiation, survival, and apoptosis within diverse tissue growth and developmental processes. The JAK enzymes are therefore essential for cytokines and growth factors since their receptors lack intrinsic kinase activity.[26] Erythropoietin and thrombopoietin are one of such growth factors, which only employ Janus-associated kinase 2 (JAK2) as cytoplasmic tyrosine kinase.[26,27] This unique and specific interaction of EPO with JAK2 therefore has drawn attention for JAK2 to be a crucial protein for definitive erythropoiesis.

Even Neonatal Polycythemia (NP) is known as physiologic and the pathways conducted to EPO, EPO receptor and subsequent intracellular signaling -including JAK2 tyrosine kinase- remain constant both for polycythemia vera and NP. However, our results for the first time showed that although the pathway is unique, polycythemic neonates are free of automated erythropoiesis and are under the effect of undisrupted erythropoiesis. Hence, it is most likely due to short-term hypoxia (at most nine months), which is associated with EPO increase while the polycythemic adults are under the effect of autonomous erythropoiesis and are independent of EPO. Within this context, we agreed that, JAK2-V617F mutation keeps its basic feature to be an acquired somatic mutation instead of congenital.[11]

As the individuals get older (about 60 years), they develop JAK2 mutation alone or in addition to other mutations seen in myeloproliferative diseases.[20,28-30] The reason why they develop mutations causing polycythemia is still unclear. Is this an adaptation to "physiological" gain of function of non-receptor protein tyrosine kinase by a single nucleotide polymorphism (SNP) as a mutation or the first step to jump to tumor development? It could easily be hypothesized that there may be other underlying predisposing factors that may lead to chronic hypoxia in adults, which last lifelong and lead to persistence by stimulation of the EPO cascade to provide sufficient tissue oxygenation. However, the results inspecting the relationship between thrombosis, leukocytosis and JAK2V617F have found to be conflicting and inconclusive by different groups of investigators.[29,31]

Furthermore, generation of Jak2 knockout mice led to defective erythropoiesis.[32] Due to this iniquity of EPO to JAK2 tyrosine kinase, an acquired V617F mutation causing auto activation of JAK2 may display its first symptom in adults as an increase in the red blood cell count instead of the myeloid series during tumor development such as leukemia. In addition, a functional Jak signaling has also been found to be essential for effective immune responses that keep the organism open to malignant transformation during tumor growth.

CONCLUSION

In conclusion, *JAK2V617F* mutation in polycythemia vera is an acquired mutation since we stated for the first time that neonates having polycythemia are lacking the *JAK2V617F* mutation. This would be clarified by further prospective stud-

ies following polycythemic neonates for the development of polycythemia vera in their future life.

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