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JAK2 Mutation Assessment in Thrombotic Events at Unusual Anatomical Sites: Insights from a High-Altitude Cohort

Husain Yahya Alkhaldy[1], Ayel Omar Yahya[2], Abdullah Mohammed Algarni[3], Omayma SE Bakheet[4], Mohammed Assiri[3], Muhammad Saboor[5,6]

[1]Department of Internal Medicine, College of Medicine, King Khalid University, Abha, Saudi Arabia; [2]Division of Adult Hematology, King Abdulaziz Medical City, Riyadh, Saudi Arabia; [3]Aseer Central Hospital, Abha, Saudi Arabia; [4]Department of Laboratory Medicine and Blood Bank, Aseer Central Hospital, Abha, Saudi Arabia; [5]Department of Medical Laboratory Sciences, College of Health Sciences, University of Sharjah, Sharjah, United Arab Emirates; [6]Research Institute for Medical and Health Sciences, University of Sharjah, Sharjah, United Arab Emirates

Correspondence: Husain Yahya Alkhaldy; Muhammad Saboor, Email halkhaldy@kku.edu.sa; M.Ahmed@sharjah.ac.ae

Introduction: Thrombosis stands as a significant contributor to both morbidity and mortality in individuals afflicted with myeloproliferative neoplasms. This retrospective study investigated the association between JAK2 mutations and venous thrombosis at unusual sites, and in young individuals with ischemic stroke, residing at high altitudes in the Aseer region, Saudi Arabia.

Patients and Methods: Data were collected from two high-altitude referral hospitals over three years (2020–2022). Records of all JAK2 mutation tests were reviewed. Those requested as part of evaluation of thrombosis events, without known myeloproliferative neoplasms (MPNs) were analysed.

Results: Among the 208 JAK2 tests, 40 (19.2%) were linked to thrombotic event evaluations. The cohort, with a median age of 41, included 17 (42.7%) males and 23 females, with 57.5% having completely normal complete blood counts (CBC). Thrombotic events were divided between splanchnic vein thrombosis (36.6%) and cerebral thrombosis (34.1%), while the remaining cases involved unprovoked deep vein thromboses/pulmonary embolisms and portal vein thrombosis. Only 2 (5%) participants tested positive for JAK2 mutations: a 17-year-old male diagnosed concurrently with polycythemia vera after renal vein thrombosis and a 31-year-old woman with hepatic vein thrombosis and a normal CBC.

Conclusion: This study reveals that JAK2 mutations are infrequently found in high-altitude patients with unprovoked DVT, PE, or atypical thrombosis. While JAK2 testing is notably relevant for splanchnic vein thrombosis, its routine use for other thrombotic events, particularly with normal CBC results, remains uncertain. Given the study's limitations, further prospective research with larger cohorts is needed to refine guidelines for JAK2 mutation testing in various thrombotic contexts.

Keywords: thrombosis, JAK2, myeloproliferative neoplasm, deep vein thrombosis

Introduction

Thrombosis, encompassing both arterial and venous events, is a significant contributor to morbidity and mortality among individuals diagnosed with myeloproliferative neoplasms (MPNs). It often serves as the initial manifestation of MPN and may precede the formal diagnosis. The predilection for thrombosis in MPNs involves commonly afflicted sites such as cerebral and coronary arteries, as well as deep veins of the lower limbs (deep vein thrombosis) and pulmonary embolism (PE). MPN-related thrombosis can also manifest in rare and distinctive ways, such as splanchnic and cerebral dural vein thromboses, with a particularly notable association seen with splanchnic vein thrombosis.[1–3] Some thrombotic events like stroke occurring in individuals under 50 years of age and venous thrombosis affecting unusual anatomical sites such as the cerebral, splanchnic, renal, and upper limb regions, necessitate a comprehensive workup exploring potential unusual etiologies.

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JAK2V617F (JAK2) constitutes a point mutation localized within the Janus kinase 2 (JAK2). Functionally, JAK2 holds a pivotal position in the intracellular transmission of signals from cytokines and growth factor receptors, thereby exerting significant influence over the inflammatory signaling cascade and the proliferation of hematopoietic cells.[4] The mutation in JAK2 brings about a perpetual state of activation within JAK2, resulting in escalated rates of cellular proliferation, differentiation, and the release of cytokines. The JAK2 mutation is a hallmark feature consistently observed in cases of polycythemia vera (PV) and a significant portion of other classical MPNs.[5–8] Its presence has been directly linked to an increased risk of thrombosis, primarily attributed to associated factors such as leukocytosis, platelet activation, and altered vascular endothelial function.[9,10] MPNs with the JAK2 mutation demonstrate a notably heightened risk of thrombosis when compared to their JAK2 unmutated counterparts, and the extent of this risk corresponds to the allele burden of the mutation, emphasizing the mutation's role in thrombotic events.[7]

Among the various thrombotic events associated with JAK2-mutated MPNs, hepatic and splanchnic vein thrombosis exhibit a well-established association with the JAK2 mutation.[1] While evidence-based guidelines exist for JAK2 mutation testing in cases of idiopathic splanchnic vein thrombosis, the precise relationship between the JAK2 mutation and thrombosis at other unusual sites remains less clear. Clinicians may opt for JAK2 mutation testing in cases of unprovoked venous thromboembolism (VTE) and VTE occurring at atypical sites in an effort to identify the underlying etiology, despite a relatively low diagnostic yield, especially in individuals with a normal complete blood count (CBC). One illustrative example of this diagnostic challenge is cerebral sinus thrombosis, a condition occurring in approximately 1% of individuals with MPNs.[11] Intriguingly, an underlying MPN is identified in only 3.8% of cases of cerebral venous thrombosis (CVT), indicating a limited direct association.[12] Furthermore, the risk of thrombosis has been consistently shown to be associated with an abnormal cell count; more with erythrocytosis but also with thrombocytosis and leukocytosis.[13–15]

High altitude is known to present unique physiological challenges to the human body, including alterations in blood composition and coagulation pathways. High altitude associated hypoxia has been reported to predispose to both idiopathic arterial and venous thrombosis in otherwise healthy and young individuals.[16,17] Idiopathic cerebral venous thrombosis has been noted at high altitude with high hemoglobin and increased D-dimer levels.[18] High altitude could also interact with other hereditary or acquired thrombophilia risk augmenting further the risk of first or recurrent thrombosis.[19]

The primary objective of this study was to investigate whether JAK2 mutation, in the absence of overt MPNs, contributes to the incidence of venous thrombosis at unusual anatomical sites, particularly in young individuals residing in high-altitude region.

Material and Methods

This was a retrospective cross-sectional laboratory based study. The study protocol was approved by Aseer Institutional Review Board {IRB (H-06-B-091, approval number REC-04-06-2022)} and was carried out in accordance with the Helsinki Declaration. Patient consent was waived off due to retrospective nature of the study based on the request of the research team. Data collected were deidentified prior to exporting into an excel sheet and were handled with strict confidentiality. We collected laboratory records for all JAK2 mutation requests made over a span of three years (2020–2022) in two referral hospitals serving a population residing at an altitude of 2270–3000 meters above sea level, Aseer region, Saudi Arabia. Requests that indicated thrombosis as a reason were considered for inclusion in the study and the laboratory data and imaging linked to these specific requests were reviewed. For CBC, EDTA anticoagulated samples were processed using Sysmex XN-3100. For JAK2 testing, RNA isolated from peripheral blood samples (using the MagNA Pure System) was reverse-transcribed, amplified, and sequenced for any mutations involving exons 12, 13, 14, or 15 using an ABI 3730 XL genetic analyzer.

Statistical analyses were conducted using Stata version 18.0. Medians and ranges are provided for continuous variables, and frequencies and percentages for categorical variables. Comparisons between groups utilized Fisher's exact test for categorical variables or the Mann–Whitney *U*-test for continuous variables.

Results

Among 208 JAK2 tests received over three years, 40 (19.2%) were requested during the evaluation of thrombotic events. Table 1 depicts the demographic and laboratory characteristics of the patients. Patients were relatively young, with a median age of 41, and the gender breakdown was 17 (42.7%) males and 23 females. Slightly more than half (n=23, 57.5%) of the cohort had normal CBC.

Thrombotic events involved the splanchnic vein thrombosis were noted in third of the patients (n=15, 36.6%) and the brain in another third (n=14, 34.1%) as shown in Table 2. The remaining thrombotic events involved nine events of unprovoked DVT/PEs and three events of renal renal vein thrombosis (Table 2). Among the study participants, only two (5%) were positive for JAK2 mutations: a 17- year-old boy who presented with renal vein thrombosis and was diagnosed with polycythemia vera and a 31-year-old lady who presented with hepatic vein thrombosis and normal CBC.

Discussion

In this study, we sought to investigate the prevalence of JAK2 mutations in patients undergoing evaluation for unusual thrombotic events; those occurring at unusual sites and stroke occurring in young population. A comprehensive analysis of 208 JAK2 tests was conducted, of which 19.2% were requested in the context of thrombotic events. The demographic profile of the cohort revealed a median age of 41 years, and a slightly unequal gender distribution, with 42.7% being males and 57.5% females. Interestingly, approximately half of the cohort presented with a normal CBC at the time of evaluation. The abnormal CBC findings were notable, with three patients exhibiting leukocytosis, 10 displaying thrombocytosis, and another 10 presenting with erythrocytosis.

Table 1 Characteristics of the Study Cohort

Characteristics	Total (40)	Men (17)	Women (23)	p Value
Age, yrs {Median (IQR)}	41 (31–46)	41 (34–48)	40 (27–45)	0.18
Splenomegaly, n (%)	3 (7.5)	1 (2.5)	2 (5)	
JAK-2 mutation, n (%)	2 (5)	1(2.5)	1(2.5)	
Red blood cells, ($\times 10^{12}$/L)	5.1 (4.5–5.7)	5.7 (5.1–6)	4.8 (4.4–5.3)	0.001
Hemoglobin g/dL	14 (11–16)	16 (15–17.9)	11.8 (10.4–14.5)	<0.001
Hematocrit, %	43 (36–49)	48.3 (46.7–51.6)	37.1 (34–43.2)	<0.001
Mean corpuscular volume, fl	82 (76–86)	84.1 (80.2–87.9)	77 (73.8–85)	0.012
Mean corpuscular hemoglobin, pg	27 (25–29)	28 (25.5–30.5)	25 (22.2–28.4)	0.016
Mean corpuscular hemoglobin concentration, g/dL	32 (31–34)	33.3 (32.2–34.7)	31.5 (29.3–32.2)	<0.001
Red cell distribution width–CV, %	15 (13–17)	13.3 (12.9–14.6)	16.4 (14.3–18.7)	0.016
White blood cell count, (×109/L)	5.9 (5.1–8.1)	5.8 (5.1–6.9)	6 (5.1–9.6)	0.57
Neutrophil count, ($\times 10^9$/L)	3.7 (2.5–6.5)	3.5 (2.3–3.8)	4.3 (2.9–12.1)	0.16
Lymphocytes count, ($\times 10^9$/L)	1.9 (1.6–2.7)	1.7 (1.7–2.7)	2.1 (1.6–2.6)	0.78
Monocyte count, ($\times 10^9$/L)	0.6 (0.4–0.68)	0.54 (0.4–0.6)	0.6 (0.44–1.3)	0.25
Basophil count, ($\times 10^9$/L)	0.04 (0.03–0.2)	0.04 (0.02–0.05)	0.05 (0.04–0.2)	0.27
Eosinophil count, ($\times 10^9$/L)	0.11 (0.09–0.21)	0.1 (0.09–0.11)	0.2 (0.09–0.22)	0.23
Platelets count, ($\times 10^9$/L)	259 (187–383)	216 (175–354)	286 (203–558)	0.12

Notes: Values of blood counts are shown as Median (IQR).

Table 2 Type of the Index Event and the Gender Distribution

Rubrics	Male	Female	Total (n=40)
Splanchnic vein thrombosis	5	9	15 (36.6%)
Unprovoked DVT/PE	4	5	9 (22%)
Cerebral sinus thrombosis	5	3	8 (19.5)
Ischemic stroke	2	4	6 (14.6%)
Renal vein thrombosis	1	2	3 (7.3%)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

The low proportion (5%) of patients testing positive for JAK2 mutations in this study (Table 1) echoes the findings of previous research, indicating that JAK2 mutations, while a hallmark of certain MPNs, are not ubiquitous in these conditions.[20] The presence of JAK2 mutation in a 17-year-old boy with renal vein thrombosis and subsequent diagnosis of polycythemia vera, though rather unusual, resonates with existing literature, as JAK2 mutations are invariably associated with polycythemia vera.[21] Several other studies have also evaluated the prevalence of JAK2 mutation in patients with thrombosis with variable results.[22–25] However, only one study reported the presence of JAK2 in patients with CVT without overt MPNs.[26] Furthermore, it has been reported that standard practice does not endorse routine JAK2 testing for individuals encountering unexplained thrombotic events, except for cases involving splanchnic vein thrombosis. For patients grappling with CVT, the significance of conducting JAK2 mutation testing remains to be conclusively determined.[27] Contrary to the above literature report, a current study found JAK2 mutations is relatively frequent among individuals experiencing cerebral venous sinus thrombosis (CSVT) and should be considered a standard screening measure within this demographic. CSVT cases in individuals carrying JAK2 mutations may exhibit a predilection for particular venous sinuses and are correlated with an elevated incidence of intracranial hemorrhage (ICH), while overall prognosis remains comparable.[11] Upon the amalgamation of data analyses from two databases by Dentali et al, the findings collectively indicate a tenuous link between CVT and MPNs. Consequently, these results imply that an exhaustive inquiry to identify an underlying MPN may not be warranted for every patient experiencing CVT without overt myeloproliferative characteristics.[20]

Over a decade, a study gathered data from patients with thrombotic events who underwent JAK2 screening. Excluding those with signs of underlying MPN, such as high hematocrit and platelet levels, the study found that 2.65% had the JAK2 mutation, with 1.1% having an allele burden of at least 2%, ultimately leading to MPN diagnoses. Age, platelet count, elevated C-reactive protein, and splenomegaly were significantly associated with JAK2 mutation, particularly emphasizing the link between splenomegaly and the mutation. These findings suggest that the JAK2 mutation is infrequent in thrombotic events without evident MPN, but splenomegaly serves as a valuable indicator for potential JAK2 mutations in patients with non-splanchnic thrombotic events, warranting further assessment and close monitoring.[28] Another study also reported low frequency of JAK2 mutation and recommended that instead of testing for JAK2 mutation, other thrombophilia causes shall be ruled out by thrombophilia profile markers.[29] However, in situations where thrombosis can be directly attributed to well-defined provoked factors, such as birth control pills or postpartum VTE, the need for extensive JAK2 mutation investigation may be unwarranted. This is because the thrombotic event can be logically linked to the established risk and the management and prevention strategies are already established in such cases.

Contrastingly, in the current study, the case of a 31-year-old woman presenting with hepatic vein thrombosis despite having a normal CBC underscores the need for a nuanced diagnostic approach. Hematological parameters alone may not capture the complexity of MPNs, necessitating comprehensive molecular testing for accurate diagnosis. The implications of JAK2 mutations in thrombosis, irrespective of an established MPN diagnosis, have been steadily unfolding in recent scientific literature.[30] There is a growing body of research that underscores the value of JAK2 mutation testing in patients who present with thrombotic events at unusual sites or in cases of unprovoked thrombosis.

This study found that a significant number of the studied participants (n=15; male 5 and female 10) for whom JAK2 mutation were tested had splanchnic vein thrombosis. The two patients who tested positive for JAK2 mutations had splanchnic vein thrombosis. High prevalence of splanchnic vein thrombosis (5–10%) in MPNs has been reported by several studies,[1,22,31] even before the development of MPNs.[32] A meta-analysis reported that splanchnic vein thrombosis was the most common clinical manifestation in patients with MPNs.[3] However, the incidence of JAK2 in unprovoked splanchnic vein thrombosis is not well reported. The findings from the small cohort unveiled a compelling narrative within the realm of thrombotic events associated with JAK2 positivity. Specifically, the discovery that both individuals who tested positive for JAK2 mutations exhibited splanchnic vein thrombosis, with one presenting an abnormal CBC and the other a normal CBC, is noteworthy. This revelation underpins the assertion that targeted JAK2 screening in cases of splanchnic vein thrombosis is not only sensible but also aligned with existing clinical guidelines.

The data we reviewed provides limited support for the routine screening of JAK2 mutations in thrombotic cases occurring outside the splanchnic realm, where the yield may not justify the expense and effort involved. This conclusion can be expounded upon by delving into relevant medical literature. The decision to consider JAK2 mutation testing should be guided by clinical context and risk factors, with a keen awareness of the diagnostic yield. As noted in our previous discussion, JAK2 mutations are notably associated with thrombosis in the splanchnic vein, and targeted screening in such scenarios aligns with established clinical guidelines.[33] The debate surrounding JAK2 screening in extrapelvic thrombosis should consider the risk-benefit balance. Screening for JAK2 mutations is not without cost and may lead to unnecessary testing and anxiety for patients.

In the realm of high-altitude habitation, it becomes evident that such altitudes wield a substantial influence on the risk for thrombotic events. This discourse embarks upon a profound exploration of the intricate relationship between elevated altitudes and an augmented vulnerability to thrombosis that elucidates the intricate mechanisms underpinning this association.[34] The predominant feature of high-altitude environment is the state of hypoxia, where oxygen levels are notably diminished. This hypoxic milieu orchestrates several critical alterations in the constituents of blood, including augmented viscosity and heightened activation of platelets, thereby fostering a predisposition to thrombotic events.[35,36] A meticulous examination of the effects of altitude on platelet function and clot formation also confirms the pro-thrombotic ramifications of hypoxia.[37] The high-altitude terrain ushers in a disruption in the coagulation cascade.[38,39] Research indicates that the hypoxic conditions prevalent at elevated altitudes contribute to an upregulation of clotting factors while simultaneously suppressing the fibrinolysis process.[40–42] This multifaceted disturbance in the coagulation pathway sets the stage for thrombosis. The denizens of high-altitude regions are subject to a compromise in endothelial function. Hypoxia imparts oxidative stress on the endothelial cells, rendering them more susceptible to inflammation and thrombus formation.[16,43,44] The high-altitude terrain introduces several local factors that further exacerbate the risk of thrombosis. The frigid temperatures prevalent at these altitudes lead to vasoconstriction, constricting arterial blood flow.[45]

This study explores the interplay between JAK2 mutations and venous thrombosis, particularly among individuals lacking overt MPNs. Despite the relatively modest prevalence of JAK2 mutations in this cohort, their clinical relevance in specific scenarios is paramount. The association between JAK2 mutations and thrombotic episodes, which may precede MPN diagnoses, underscores the need for judicious consideration during thrombosis evaluation, particularly at unusual anatomical sites. While JAK2 screening remains a justifiable course for patients with splanchnic vein thrombosis, its utility in routine testing beyond this context proves to be diagnostically limited. In the intricate realm of thrombotic disorders, especially in the absence of overt MPNs, clinicians encounter diagnostic conundrums. Clinicians typically resort to JAK2 testing after thoroughly exploring other potential causes, which may encompass deficiencies in factors like protein C, protein S, and antithrombin. Although JAK2 mutations serve as valuable indicators, their applicability to routine testing for thrombosis at atypical sites, including cerebral vein thrombosis, remains enigmatic. This study accentuates the exigency of further research to refine diagnostic paradigms and optimize patient care. As we navigate the dynamic crossroads of genetics, thrombosis, and clinical praxis, this investigation augments our comprehension of the intricate interrelationship between JAK2 mutations and thrombotic incidents. Sustained research endeavors and interdisciplinary collaboration within the medical domain will undoubtedly furnish holistic insights, augmenting our

proficiency in addressing the idiosyncratic diagnostic and therapeutic requisites of patients grappling with thrombotic complexities absent overt MPNs.

The study bears inherent limitations owing to its retrospective nature and a relatively small patient sample size. It is conceivable that a considerable portion of individuals with idiopathic venous thromboembolism, thrombosis at anatomically atypical locations, and young individuals experiencing ischemic strokes, were potentially not subjected to JAK2 mutation screening. This lack of screening might be attributed to multiple factors, such as the presence of unremarkable CBCs, the specific medical specialty under which they received care, or the preferences of attending physicians.

Keeping in view the findings of this study and detailed discussion, it is recommended that future research should be focus on developing clear guidelines for selecting patients for JAK2 testing, particularly those with unusual thrombotic events. Prospective, multicenter studies across diverse populations, especially at high altitudes, would help validate our findings and assess the role of environmental factors. Research should also aim to establish risk profiles based on clinical features, biomarkers, and extended genetic screening to optimize patient selection. Longitudinal studies to follow JAK2-positive patients without overt MPNs would further clarify long-term outcomes and the need for continued monitoring.

Conclusion

This retrospective analysis indicates that JAK2 mutations are relatively rare among high-altitude patients presenting with unprovoked DVT, PE, or thrombosis at atypical anatomical sites. Our findings suggest that while JAK2 mutation testing is notably associated with splanchnic vein thrombosis, its utility in routine testing for other thrombotic events, particularly outside the splanchnic system and with normal CBC results, is less clear. Given the small sample size and the limitations inherent in a retrospective study, these results should be interpreted with caution. Future prospective studies with larger cohorts are necessary to better define the role of JAK2 mutation testing in various thrombotic scenarios and to establish more precise guidelines for its application in clinical practice.

Data Sharing Statement

Data will be made avialable from The first author/ corresponding author; Husain Alkhaldy (halkhaldy@kku.edu.sa).

Ethical Approval

The study protocol was approved by Aseer institutional review board {IRB (H-06-B-091, approval number REC-04-06-2022)} and was carried out in accordance with the Helsinki Declaration. Ethical approval was waived off due to retrospective nature of the study based on the request of the research team.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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