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Role of JAK2V617F Mutational Screening in Detecting Occult Myeloproliferative Neoplasms in Egyptian Patients with Budd-Chiari Syndrome

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Abstract

Background: Budd-Chiari Syndrome (BCS) is a life-threatening hepatic disorder caused by complete or partial obstruction of hepatic venous outflow. This study aimed to detect JAK2V617F mutation in Egyptian patients with BCS and its value in detection of occult Myeloproliferative Neoplasms (MPNs).

Material and Method: The study was carried out on 57 newly diagnosed BCS patients. Thrombophilia screening tests were performed in all patients including prothrombin G20210A mutation, Methyltetrahydrofolate Reductase (MTHFR) mutation, Factor V Leiden mutation, measurement of Antithrombin 3 (AT3), protein C functional activity, free protein S antigen, and antiphospholipid antibodies/lupus anticoagulant, in addition to detection of JAK2V617F mutation by real time polymerase chain reaction.

Results: In our study 35.1% of BCS patients had idiopathic etiology while 64.9% were secondary to other pro-thrombotic factors; the most common was MTHFR mutation (42.1%) followed by FV Leiden (29.8%) while JAK2V617F mutation was positive in 21.1% of cases, it was detected in 41.7% of patients with idiopathic BCS and in 58.3% with secondary pro-thrombotic factors with no significant relation between pro-thrombotic risk factors and JAK2V617F mutation (p= >0.005). JAK2V617F mutational screening in BCS had raised percentage of MPN as a cause for BCS from 15.8% to 24.6% when occult cases were added.

Conclusion: The JAK2V617F mutation is an acquired mutation associated with occult MPNs that can be used for diagnosis of latent MPNs presenting with thrombotic events.

Keywords: Budd-chiari syndrome (BCS); Myeloproliferative neoplasms (MPNs); JAK2V617F mutation

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Introduction

Budd-Chiari Syndrome (BCS) is a life-threatening hepatic disorder caused by complete or partial obstruction of hepatic venous outflow [1]. The presentations range from acute, chronic liver failure and cirrhosis to completely asymptomatic patient (15% to 20%) [2]; therefore, can be fatal if the underlying etiological factors are not diagnosed and treated. Accordingly; BCS is classified as being primary (intravascular thrombosis) or secondary (extravascular compression) [3]. In Egyptian patients; Factor V Leiden is the most common cause (in 53% of cases) [4], while in European countries, it is found in 12% to 31% of BCS cases, other inherited pro-thrombotic risk factors [G20210A Prothrombin gene, MTHFR mutation, protein C and protein S deficiency] are less common. Antiphospholipid syndrome (15% of cases) and oral contraceptives (50%) are the most common acquired/external etiologic factor [1].

Clonal disorders of hematopoiesis, as Philadelphia chromosome negative Myeloproliferative Neoplasms (MPNs) are etiologic factors in a significant proportion of BCS case (35% to 50%) [5,6]. It has been suggested that up to 87% of idiopathic BCS is caused by occult MPNs (i.e. lack typical hematologic features) [7], those cases increase the prevalence of MPNs to 45% to 53% of BCS patients [5]. The distinction between thrombophilia abnormalities and MPNs as etiological factors may have important clinical implications due to different treatment modalities [8]. Detecting

Table 1: Description of demographic, clinical and laboratory data.

Parameter			Number (%)
Sex	Male		23 (40.4%)
	Female		34 (59.6%)
	Male: Female ratio		01:01.0
History	Thrombosis in other sites		7 (12.3%)
	Oral/Genital ulcer		9 (15.8%)
Clinical presentation	Acute		10 (17.5%)
	Subacute		11 (19.3%)
	Chronic		36 (63.2%)
Etiology	Idiopathic		20 (35.1%)
	Secondary causes		37 (64.9%)
Secondary causes	Protein C deficiency		3 (5.3%)
	Protein S deficiency		1 (1.8%)
	MPN		14 (24.6%)
		Overt	9 (15.8%)
		Occult	5 (8.8%)
	FVL mutation		17 (29.8%)
	Type of FVL mutation	Homozygous	3 (17.6%)
		Heterozygous	14 (82.4%)
	Prothrombin G20210A Mutation		2 (3.5%)
	MTHFR mutation		24 (42.1%)
	Type of MTHFR Mutation	Homozygous	1 (2.5%)
		Heterozygous	23 (95.5%)
	JAK2 V617F mutation		12 (21.1%)
	Type of JAK2 V617F mutation	Homozygous	2 (16.7%)
		Heterozygous	10 (83.3%)
	Antiphospholipid antibody syndrome		8 (14%)
	Behcet disease		10 (17.9%)
	Hormonal therapy		5 (8.8%)
	Pregnancy		7 (12.3%)
Location of thrombosis by doppler Ultra sound	MHV thrombosis		48 (84.2%)
	RHV thrombosis		50 (87.7%)
	L HV thrombosis		52 (91.2%)
	PV thrombosis		2 (3.5%)
	IVC thrombosis		9 (15.8%)
Immunologic markers	Anticardiolipin IgM		4 (7%)
	Lupus anticoagulant		7 (12.3%)
Parameter			**Range [(Mean ± SD) or (Median IQR)*]**
Age (years)			13-55 (27.91 ± 8.13)
CBC parameters	Hb (g/dl)		7-17 (12.24 ± 2.4)
	TLC (×10^9/L)		1.6-26 [7.3 (5-10.9)*]
	Platelets (×10^9/L)		37-909 (234.6 ± 189.52)
Coagulation profile	PT (seconds)		11-34 (14.36 ± 3.84)
	INR		0.90-2.50 (1.28 ± 0.34)
	PTT (seconds)		26-65 (30.49 ± 8.68)

MPN: Myeloproliferative Neoplasia; FVL: Factor V Leiden; MTHFR: Methyletetrahydrofolate Reductase; JAK2 V617F: Janus Kinase 2 V617F; MHV: Main Hepatic Vein; RHV: Right Hepatic Vein; LHV: Left Hepatic Vein; PV: Portal Vien; IVC: Inferior Vena Cava; IgM: Immunoglobulin M; CBC: Complete Blood Picture; Hb: Hemoglobin; TLC: Total Leucocytic count; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; INR: International Normalized Ratio; SD: Standard Deviation; IQR: Interquartile Range

JAK2V617F mutation is the first diagnostic step for diagnosing MPNs underlying a BCS as its diagnosis at time of acute thrombosis and during post thrombotic period is often problematic [9]. Janus kinase 2 is a cytoplasmic tyrosine kinase that transduces signals triggered by hematopoietic growth factors such as erythropoietin in normal and neoplastic cells [5]. It has been detected in 37% to 45% of all BCS patients [1]. JAK2V617F mutation could be a pro-coagulant to thrombosis even without MPNs owning to involvement in heparanase up regulation *via* Erythropoietin (Epo) receptor with subsequent activation of coagulation system [10]. Thus this study aimed to detect JAK2V617F mutation in Egyptian patients with BCS and its value in detection of occult MPNs.

Material and Methods

This study was conducted at Ain Shams University Hospitals during the period from July 2017 to July 2018, and was approved by the local ethics committee and was conducted in accordance with the declaration of Helsinki and written informed consent was provided by all participants. The study was carried out on 57 newly diagnosed BCS patients, all were subjected to complete history taking stressing on transients risk factors for venous thromboembolism (surgery, oral contraceptive use, trauma and prolonged immobilization). Doppler

Table 2: Comparison between negative and positive JAK2 V617F mutation cases as regard demographic, clinical and laboratory data.

Parameter			JAK2 V617F positive (n=12) Number (%)	JAK2 V617F negative (n=45) Number (%)	P Value	Sig
Age (years)			31.17 ± 6.75	27.04 ± 8.31	0.119*	NS
Sex	Male		6 (26.1%)	17 (73.9%)	0.517**	NS
	Female		6 (%17.6)	28 (82.4%)		
Organomegaly	Hepatomegaly		11 (91.7%)	37 (82.2%)	0.667**	NS
	Splenomegaly		8 (66.7%)	29 (64.4%)	1.0**	NS
History	Thrombosis in other sites		1 (8.3%)	6 (13.3%)	1.0**	NS
Etiology	Idiopathic		5 (41.7 %)	15 (33.3%)	1.0**	NS
	Secondary causes		7 (58.3 %)	30 (66.7%)		
Secondary Causes	Protein C deficiency		1 (8.3%)	2 (4.4%)	0.51**	NS
	Protein S deficiency		0 (0.0%)	1 (2.2%)	1.0**	NS
	MPN		12 (100%)	2 (4.4%)	0.001**	HS
	Type of MPN	Overt	7 (58.3)	2(4.4%)		
		Occult	5 (41.7)	0(0%)		
	FVL mutation		2 (%16.7)	15 (33.3%)	0.31**	NS
	Prothrombin G 20210A mutation		0 (0%)	2 (4.4%)	1	NS
	MTHFR mutation		4 (33.3%)	20 (44.4%)	0.489*	NS
	Antiphospholipid antibody syndrome		2 (16.7%)	6 (13.3%)	0.670**	NS
	Behcet disease		2 (16.7%)	8 (18.2%)	1.0**	NS
	Hormonal therapy		1 (8.3%)	4 (8.9%)	1.0**	NS
	Pregnancy		7 (15.6%)	0 (0.0%)	0.32**	NS
Location of thrombosis by doppler Ultra sound	MHV thrombosis		11 (91.7%)	37 (82.2%)	0.667**	NS
	RHV thrombosis		38 (84.4%)	12 (100%)	0.325**	NS
	LHV thrombosis		40 (88.9%)	12 (100%	0.573**	NS
	PV thrombosis		0 (0%)	2 (4.4%)		
	IVC thrombosis		2 (16.7%)	7 (15.6%)	1.0**	NS
parameter			mean ± SD	mean ± SD		
Age (years)			31.17 ± 6.75	27.04 ± 8.31	0.119*	NS
CBC parameters	Hb (g/dl)		13.32 ± 2.96	11.96 ± 2.18	0.08*	NS
	TLC ($\times 10^9$/L)		8.43 ± 3.17	8.19 ± 4.88	0.87*	NS
	Platelets ($\times 10^9$/L)		317.92 ± 254.12	212.38 ± 194.84	0.09*	NS

JAK2 V617F: Janus Kinase 2 V617F; N: Number; Sig: Significance; MPN: Myeloproliferative Neoplasia; FVL: Factor V Leiden; MTHFR: Methyletetrahydrofolate Reductase; MHV: Main Hepatic Vein; PV: Portal Vien; IVC: Inferior Vena Cava; CBC: Complete Blood Picture; Hb: Hemoglobin; TLC: Total Leucocytic Count; SD: Standard Deviation; *Student t test; **Fisher exact test; HS: Highly Sensitive

ultrasound was performed for evaluation of IVC and hepatic veins. Complete blood picture and coagulation profile (PT/INR, APTT) were done for all patients.

Thrombophilia screening tests were performed in all patients including prothrombin G20210A mutation, MTHFR mutation, Factor V Leiden mutation, measurement of Antithrombin 3 (AT3), protein C functional activity, free protein S antigen, and antiphospholipid antibodies/lupus anticoagulant. Detection of JAK2V617F mutation by Real Time Polymerase Chain Reaction (RT-PCR) using slang 96 p real time PCR system (SANSURE BIOTECH INC, China) using ipsogen JAK2 MutaScreen kit; in which 2 TaqMan probes were used labeled with a fluorescent dye at its 5 end such as FAM or VIC, generation of fluorescent signal only with FAM dye indicating homozygous mutation while generation of fluorescent signal from FAM and VIC indicate heterozygous mutation. V617F positive control, negative control and cutoff samples were used. The FAM/VIC ratios for all the samples, Positive Control (PC), Cut-Off Sample (COS), and Negative Control (NC) were calculated.

The Normalized Ratio (N Ratio) for the Cut-Off Sample (COS) and for all the samples were calculated as the following: N Ratio Sample=Ratio Sample/Ratio NC. The gray zone around the normalized ratio of the COS was calculated as following: (N Ratio COS) = [(N Ratio COS × 0.94): (N Ratio COS × 1.06)]. Interpretation of genotyping results using normalized ratio was as the following [11] (Table S1).

Statistical analysis

All data were analyzed using SPSS Version 20.0. (Armonk, NY: IBM Corp). Data are expressed as mean ± Standard Deviation (SD) or frequency and percentage as appropriate. Differences in discrete variables between groups were evaluated using the chi-square, student T or fishers exact tests according to sample size.

Results

Out of 57 BCS patients; 23 (40.4%) were males and 34 (59.6%) were females, their ages range from 13 to 55 years. Patients were divided according to etiology of intravascular thrombosis into 2 groups; 20/57 (35.1%) of idiopathic etiology and 37/57 (64.9%) secondary to other pro-thrombotic factors; the most common was MTHFR mutation (421%) followed by Factor V Leiden mutation (29.8%) and MPN (24.6%). Concerning site of thrombosis 52 (91.2%) had Left Hepatic Vein (LHV) thrombosis, 50 (87.7%) with Right Hepatic Vein (RHV) thrombosis and 48 (84.2%) cases with Main Hepatic Vein (MHV) thrombosis. The participants' demographic, clinical and hematological laboratory data are summarized in (Table 1).

Table 3: Comparison between idiopathic and secondary cases as regard demographic and laboratory data.

Parameter		Definite etiology		P value	Sig
		Idiopathic (n=20)	Secondary (n=37)		
		Number (%)	Number (%)		
Sex	Male	4 (17.4%)	19 (82.6%)	0.036*	S
	Female	15 (44.1%)	19 (55.9%)		
		(Mean ± SD) or (Median IQR)**]	Mean ± SD) or (Median IQR)**]		
Age (years)		28.9 ± 11.3	27.4 ± 6.1	0.524	NS
Hb (g/dl)		11.5 ± 1.9	12.6 ± 2.6	0.121	NS
TLC (x10^9/L)		6(4.4-8.9)**	8.8 (5.1-12)**	0.03	S
Platelets (x10^9/L)		182.4 ± 106.4	260.7 ± 216.2	0.143	NS
JAK2 V617F positivity		5 (41.7%)	7 (58.3%)	1.0*	NS

SD: Standard Deviation; IQR**: Interquartile Range; *Student t test; Sig: Significance; JAK2 V617F: Janus Kinase2 V617F; Hb: Hemoglobin; TLC: Total Leucocytic Count

JAK2V617F mutational status in relation to clinical and laboratory parameters

JAK2V617F mutation was detected in 12/57 (21.1%) BCS patients {10 (83.3%) were heterozygous and 2 (16.7%) were homozygous for mutation}. Forty five (78.9%) were negative. On comparing JAK2V617F positive and negative groups, there was a highly statistically significant relation (p=0.001) regarding MPNs diagnosis. Nine out of 57 (15.7%) BCS patients had overt MPNs (5 with Polycythemia Rubra Vera [PRV] and 4 with Essential Thrombocytosis [ET]) while 5 (8.7%) cases with occult presentation, all of them showed JAK2V617F mutation (100%), while in overt MPNs patients, the mutation was detected in 7 (77.8%) cases and the remaining 2 (22.2%) had wild type mutation (the diagnosis depended on other WHO criteria for PRV and ET). JAK2V617F mutational screening in BCS had raised percentage of MPN as a cause for BCS from 15.8% to 24.6% when occult cases were added (Table 2).

Comparison between idiopathic and secondary cases as regards demographic and laboratory data

As regards etiology of thrombosis, comparison between idiopathic 19 (33.3%) patients and secondary 38 (66.7%) patients showed significant difference as regard sex (p=0.036) with high female predominance in idiopathic patients and total leucocytic count (p=0.03), being high in secondary cases. JAK2V617F mutation was positive in 5/20 (41.7%) of the patients with idiopathic BCS and in 7/37(58.3%) of the patients with secondary BCS but with no significant difference (p=1.0) (Table 3).

Discussion

BCS is a hepatic venous out flow tract obstruction. Thrombophilia abnormalities and clonal hematopoiesis disorders as Philadelphia chromosome negative MPNs are two main mechanisms of thrombosis in a significant proportion of BCS. The diagnosis of MPNs in patients with BCS is often problematic owning to the changes that mask blood cell counts used for diagnosing MPNs and are termed occult MPNs [12]. Our study on 57 BCS patients revealed that the disease was more prevalent in females (59.6%), especially in patients with idiopathic etiology similar to another studies [3,13], this slight female predominance may be attributed to pregnancy and OCP taken. The majority of the patients (63.2%) were presented in chronic phase; concerning the site of vascular involvement by duplex ultrasonography, the LHV obstruction was found in majority of patients while associated PC and IVC thrombosis were found in 3.5 % and 15.8% of patients respectively, in contrast to other study done by Chandrasekaran et al. [14], who reported higher percentage of combined obstruction of hepatic veins and IVC in 41/71 (57.74%), this difference may be due to ethnic variation.

Table S1:

Results	Interpretation
$NRatio_{Sample} > NRatio_{cos} \times 1.06$	JAK2 V617F is detected
$NRatio_{Sample} < NRatio_{cos} \times 0.94$	JAK2 V617F is not detected
$NRatio_{Sample}$ within $NRatio_{cos}$ GZ	Result inconclusive

In our study 35.1% of BCS patients had idiopathic etiology while 64.9% were secondary to other pro-thrombotic factors; the most common was MTHFR mutation (42.1%) of whom 95.5% with heterozygous mutation; followed by FV Leiden (29.8%) of whom 82.4% with heterozygous mutation and 17.6% with homozygous one, this was similar to study done by EL Sebay et al. [13], in contrast Saker et al. [4], reported that FV Leiden was the most common secondary factor (53.1%) followed by MTHFR gene mutation with higher incidence of homozygous mutation 15.6% and 13.3% respectively. In our study JAK2V617F mutation was positive in 21.1% of the studied patients of whom 83.3% were heterozygous and 16.7% were homozygous for the mutation and this was consistent with other studies while EL Sebay et al. [4,15], identified only 11.4% (4/35 patients) with the mutation. Other studies had detected lower percentages of JAK2 mutation 2.3% and 4.3% respectively, but this could be attributed to different method of detection used and different ethnic group with different prevalence of MPNs [16,17].

Overt MPNs (fulfill all who 2016 diagnostic criteria) were found in 15.8% of which 77.8% with JAK2V617F mutation, while 8.8% of patients presented with occult disease, all of them (100%) had JAK2V617F mutation. Karakose et al. [5], found significant relation between JAK2V617F mutation and both MPNs and FV Leiden mutation, where heterozygous FVL mutation was found in all MPNs patients with JAK2V617F mutation, in contrast; in this study there was no significant relation between pro-thrombotic risk factors and JAK2V617F mutation except for MPNs.

JAK2V617F mutation was detected in 41.7% of patients with idiopathic BCS and in 58.3% with secondary pro-thrombotic factors similar to study done by Sarid et al. [18], however in our study there was no significant association between JAK2V617F mutation and either clinical presentation or hematological/coagulation parameters (CBC, PT & APTT) and the location of thrombosis. According to Karakose et al. [5], overt MPNs are observed in 23% to 31.2% of BCS patients which increases to 45% to 53% when occult cases are included as an etiological factor, in this study occult MPNs was found in 41.7% of JAK2V617F positive patients and this raise MPNs percentage as etiologic factor for BCS from 15.8% to 24.6%.

In conclusion the JAK2V617F mutation is an acquired mutation associated with occult MPNs that can be used for diagnosis of latent MPNs presenting with thrombotic events, thus it is recommended to include JAK2V617F gene analysis in the research panel for BCS patients in our institution with further studies to detect patient prognosis with this mutation and benefit from treatment with JAK2 inhibitors either alone or with other antithrombotic and cytoreductive therapies.

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