Received: 4 November 2019 | Revised: 30 January 2020 | Accepted: 20 February 2020

DOI: 10.1111/ijlh.13184

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

JAK2V617F mutation prevalence on Chilean adults suffering from primary mesenteric and portal venous thromboses

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Abstract

Introduction: Mesenteric and portal venous thromboses are rare diseases with high mortality rates and are strongly associated with hepatic cirrhosis, and abdominal inflammatory or tumoral processes, but in some cases can be the first sign of myeloproliferative neoplasm (MPN) or hereditary thrombophilia. JAK2V617F mutation detection is an important diagnostic tool for MPN patients. The aim of this study was to describe the JAK2V617F mutation prevalence on Chilean patients suffering from a primary splanchnic venous thrombosis (SVT), in order to assess how it relates to primary MVT and PVT in our specific population.

Methods: A retrospective observational study was conducted in patients referred to the University of Chile Clinical Hospital with mesenteric and/or portal venous thrombosis diagnosis over a 7-year period. Patients with primary thrombosis underwent hereditary thrombophilia study and JAK2V617F mutation screening.

Results: A total of 123 patients had splanchnic venous thrombosis (mesenteric and/or portal) as their main discharge diagnosis. Sixty patients (49%) had primary mesenteric or portal venous thrombosis (no attributable secondary cause). Hereditary thrombophilia and MPN were diagnosed in 21.6% and 43.3% of SVT patients, respectively. Twenty SVT patients remained without an etiologic diagnosis. In MPN patients, almost all had the JAK2V617F mutation (92.3%). About 16% of patients who had positive JAK2V617F mutation did not meet diagnostic criteria for MPN.

Conclusions: In this Chilean cohort, half of mesenteric or portal venous thrombosis showed no secondary cause. In this group, the main causes were MPN and hereditary thrombophilia. Nearly, all MPN patients had JAK2V617F mutation, but there was a group of patients having JAK2V617F mutation but did not meet MPN criteria.

KEYWORDS

hereditary thrombophilia, JAK2V617F mutation, mesenteric/portal vein thrombosis, myeloproliferative neoplasms

1 | INTRODUCTION

Mesenteric venous thrombosis (MVT) and portal venous thrombosis (PVT) are uncommon diseases that carry high associated mortality rates, which range from 20% to 50%.[1] Both conditions are classically associated with cirrhosis, being their incidence in this group of patients up to 16%, and in patients with concomitant hepatocellular carcinoma up to 35%.[2] Myeloproliferative neoplasms (MPN) appear

to be an important cause of primary mesenteric or portal venous thrombosis, being found in approximately 32% of these patients.[3,4]

During PVT, portal hypertension is virtually a constant feature, and both the subsequent hypersplenism and hemodilution can lead to a decreased accuracy of blood cell counts and splenomegaly for MPN diagnosis. Several series have shown that JAK2V617F detection could be useful for MPN diagnosis in MVT or PVT patients.[5-7]

Janus kinase is a family of intracellular nonreceptor tyrosine kinases that transduce cytokine-mediated signals. This family consists of 4 members: JAK1, JAK2, JAK3, and TYK2. Specifically, JAK2 plays a crucial role in signal transduction from multiple hematopoietic factor receptors.[8] This role may be disrupted by JAK2 alterations, such as a somatic mutation in the JAK2 gene that has been reported in patients with MPN,[9,10] consisting in a substitution of valine to phenylalanine at position 617 in the pseudokinase (JH2) domain of JAK2 (JAK2V617F).[10] This mutation is detected in 95% of patients with polycythemia vera and in 50%-60% of those with essential thrombocythemia and primary myelofibrosis, it is unusual to find in other myeloid diseases.[11] At a cellular level, JAK2V617F mutation leads to constitutive tyrosine phosphorylation activity that promotes cytokine hypersensitivity and induces erythropoietin-independent endogenous erythroid colony formation [9,11]

Although myeloproliferative neoplasms are considered an important cause of venous thrombosis, in up to 25%-65% of cases, MPN may not be revealed in this initial presentation, in which patients may display normal blood counts.[2,12] In the past, the diagnosis of this patient subset was extremely demanding, depending on red blood cell mass measurement, bone marrow examination, in vitro spontaneous erythroid colony formation, and serum erythropoietin measurement. Nowadays, JAK2V617F has become a routine diagnostic tool in the diagnosis of MPN.[13]

A previous meta-analysis shows significant heterogeneity among studies when describing the prevalence of JAK2V617F mutation in patients with SVT, which can range between 5% and 74%.[14] Thus, the major aim of this study was to describe the JAK2V617F mutation prevalence on Chilean patients suffering from a primary splanchnic venous thrombosis (SVT), in order to assess how it is related to primary MVT and PVT in our specific population.

2 | MATERIALS AND METHODS

A retrospective observational study was conducted in patients referred to the University of Chile Clinical Hospital with mesenteric and/or portal venous thrombosis diagnosis, over a 7-year period from 2008 to 2015. All patients having SVT within their main discharge diagnoses (CIE-10: I-81) were selected.

Medical records were analyzed, and the following data were recorded: demographic characteristics—age, gender, previous consumption of drugs, and cardiovascular risk factors; and concomitant diseases to thrombosis, such as intra-abdominal inflammatory process and solid intra-abdominal tumors. MPN diagnosis was established with standard diagnosis criteria,[15] requiring determination of patients' blood count, erythropoietin level, and bone marrow biopsy. Patients with newly diagnosed mesenteric or portal venous thrombosis and with no identified secondary cause (primary splanchnic venous thrombosis) underwent hereditary thrombophilia and JAK2V617F mutation screening. Hereditary thrombophilia screening was made with identification for paroxysmal nocturnal hemoglobinuria, antiphospholipid syndrome, hyperhomocysteinemia, protein C and S deficiency, mutation of prothrombin gene, and antithrombin III deficiency. JAK2V617F mutation screening was made using two independent PCR-based assays on DNA obtained from peripheral white blood cells. All numerical calculations and registries were performed with GRAPHPAD PRISM 5.0.

TABLE 1 Patients with splanchnic vein thrombosis (SVT) between 2008 and 2015, who consulted to the University of Chile Clinical Hospital

N	123	
Age (years)	56.72 ± 2.43	
Female sex (n, %)	68 (55.3%)	
Associated diseases to SVT	**n**	**%**
Hepatic Cirrhosis (n, %)	19	15
Recent intra-abdominal surgery within 6 mo (n, %)	16	13
Intra-abdominal solid tumor	15	12
Intra-abdominal inflammatory process	13	11
Primary SVT	60	49
Affected vein	**n**	**%**
Portal vein	27	22
Mesenteric vein	47	38
Portal, mesenteric, and/or splenic vein	38	31
BCS	8	6
Hepatic vein	1	1
Splenic vein	2	2

Note: All SVT, no tumor, and/or chronic liver disease associated with SVT was classified as primary SVT, and patients underwent screening for hereditary thrombophilia and JAK2V617F detection mutation. Intra-abdominal inflammatory process: appendicitis, diverticulitis, pancreatitis, cholecystitis. Intra-abdominal solid tumor: colon, ovary, pancreas, gastric, and bile duct.

Abbreviation: BCS, Budd-Chiari syndrome.

3 | RESULTS

A total of 265,089 patients consulted between 2008 and 2015 at the University of Chile Clinical Hospital, and 123 (0.04%) had mesenteric and/or portal venous thrombosis as the main discharge diagnosis. The average age at diagnosis was 56.72 ± 12.43 years. About 55.3% were female (n = 68). 15% had thrombosis associated with hepatic cirrhosis, and 13% were associated with recent intra-abdominal surgery. Mesenteric and/or portal venous thrombosis was the first presentation of intra-abdominal solid tumor in 12% of patients, being the most frequent ovarian and colon cancers (3.36% frequency each)

TABLE 2 Patients with primary splanchnic vein thrombosis (SVT) between 2008 and 2015, who consulted to the University of Chile Clinical Hospital

N	60	
Age (years)	53.85 ± 4.39	
Female sex (n, %)	41 (68.33%)	
Hereditary thrombophilia	**13 (22%)**	
Prothrombin gene mutation A20210G (n, %)	1 (2%)	
Protein S deficit (n, %)	2 (3%)	
Protein C deficiency (n, %)	5 (7%)	
Factor V Leiden mutation (n, %)	4 (8%)	
Hyperhomocysteinemia (n, %)	1 (2%)	
Myeloproliferative neoplasms	**26 (43.3%)**	
Essential thrombocythemia (n, %)	12 (23%)	
	JAK2V617F positiveT	*JAK2V617F negative*
	11	1
Polycythemia vera (n, %)	5 (8.3%)	
	JAK2V617F positive	*JAK2V617F negative*
	5	0
Primary myelofibrosis (n, %)	4 (6.6%)	
	JAK2V617F positive	*JAK2V617F negative*
	4	0
Latent MPN (JAK2V617F mutation positive)	5	
JAK2V617F and hereditary thrombophilia (n, %)*	**1 (1.6%)**	
No thrombophilia, MPN neither JAK2V617F mutation (n, %)	**20 (33.3%)**	

Note: n = 60. Primary SVT was defined as SVT without associated disease (intra-abdominal tumor or inflammatory process, no recent surgery, and no chronic liver disease).

*Thrombophilia of the patient was protein C deficiency. MPN: myeloproliferative neoplasms.

(Table 1). The most common affected vein was mesenteric vein (38%), portal vein (22%), and combined portal, mesenteric, and/or splenic vein (31%). Budd-Chiari syndrome was diagnosed in 8 patients (7%).

Sixty patients (49%) had SVT, and all of those patients underwent hereditary thrombophilia study and JAK2V617F mutation detection screening. The median age of those patients was 53.85 ± 4.39, and 68% were female (Table 2). Primary hereditary thrombophilia was diagnosed in 21.6% of those patients, and the most common thrombophilia associated with SVT was protein C deficiency (7%) and Factor V Leiden mutation (7%). We found 26 patients with primary SVT and JAK2V617F mutation (43.3%). We identified MPN in 26 patients, being essential thrombocytopenia the most common MPN diagnosed in patients with SVT, followed by polycythemia vera and primary myelofibrosis (Table 2). We found 1 patient with SVT, JAK2V617F mutation, and hereditary thrombophilia (protein C deficiency). In 20 (33.3%) of SVT patients, no hereditary thrombophilia, MPN, or JAK2V617F mutation was identified.

4 | DISCUSSION

As reported in the literature, a high association was found between mesenteric or portal venous thrombosis and secondary causes, such as cirrhosis, intra-abdominal inflammatory processes, recent surgery, and intra-abdominal solid tumors. There were 49% of patients who did not present a secondary cause, being diagnosed with SVT. In these patients, we found 21.6 and 33.3% of hereditary thrombophilia and MPN, respectively. It is interesting to point out that there were 5 patients (8.3% of patients with primary SVT) who did not meet the MPN criteria but had the JAK2V617F mutation, thus being classified as *latent* MPN. The approach to these patients is challenging, and further studies may clarify the evolution of latent MPN. This study strengthens the adequacy of JAK2V617F testing in Chilean patients suffering from PVT and MVT and with no secondary cause. Almost a third of the patients had molecular evidence suggesting MPN, highlighting the importance of these diseases as a life-threatening intra-abdominal thrombosis cause, even when being clinically latent and not diagnosable with conventional criteria. Testing for JAK2V617F can be performed on DNA from peripheral blood mononuclear cells with a high degree of reproducibility, but bone marrow examination is still an important part of the evaluation.

It has been previously suggested that inherited or acquired thrombophilias may have a triggering role in mesenteric or portal venous thrombosis.[2] Factor V mutation has been strongly associated with Budd-Chiari syndrome, while prothrombin gene polymorphism has been associated with portal vein thrombosis.[16,17] In our study, 21,6% of patients with splanchnic venous thrombosis and no other known

risk factors were diagnosed with a primary hereditary thrombophilia, being this percentage below what other published data suggest.[17,18] The most common disorders were protein C deficiency (n = 4.7%) and Factor V Leiden mutation (n = 4, 7%). It is important to keep in mind that the diagnosis of proteins C and S and antithrombin deficiencies needs to be interpreted with care, as acquired deficiencies can develop in cases of hepatic cirrhosis, acute thrombosis, and anticoagulant therapy.

As discussed earlier, SVT is a multifactorial disease and the coexistence of several risk factors is not uncommon. In our study, we found one patient who tested positive for both the JAK2V617F mutation and hereditary thrombophilia. Other setting data[19] suggest that this specific combination of risk factors may have an additive interaction; patients with JAK2 mutation and thrombophilia have a relative risk of 5.0 when compared to patients with no JAK2 mutation nor thrombophilia.[18]

Although the presence of the calreticulin (CALR) mutation was not evaluated in the present study, it should be noted that results of a meta-analysis suggest that screening for CALR mutations may have a role in SVT patients with a high probability of MPN in whom the JAK2V617F mutation has been excluded.[20] Thus, we will have in mind the screening for CALR mutation in this specific group of patients in the future.

In summary, these data provide the first characterization of mesenteric or portal venous thrombosis patients in the Chilean population and may help clinicians to confront this challenging pathology in this particular group.

ACKNOWLEDGEMENTS

There are no funders for this work. We would like to detail the contribution of each author to this paper. Jaime González-Montero conceived of the presented idea and wrote the main manuscript draft. Arnaldo Marín Valdés and Guillermo Conte Lanza were both part of the data recollection process. Lucía Del Valle Batalla helped with the article writing and submission. Raúl Castillo Astorga worked on statistic analysis.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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How to cite this article: González-Montero J, Del Valle-Batalla L, Castillo-Astorga R, Marín Valdés A, Conte Lanza G. JAK2V617F mutation prevalence on Chilean adults suffering from primary mesenteric and portal venous thromboses. *Int J Lab Hematol*. 2020;42:331–334. https://doi.org/10.1111/ijlh.13184