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Jak2 mutation expands the thrombophilic panel in children

Cristina Forest[a], MD, Paola Gallo[b], MD, Adriana Fumarola[b], MD, Roberta Burnelli[c], MD, Agnese Suppiej[a], MD, PhD

Affiliations: [a]Department of Medical Science, Pediatric Section, University of Ferrara, Italy; [b]Department of Medical Science, Pediatric Section, Sant'Anna Hospital, Ferrara, Italy; Pediatric Onco-hematology Unit, Sant'Anna Hospital, Ferrara.

Address correspondence to: Agnese Suppiej, Department of Medical Science, Pediatric Section, University of Ferrara, Italy, via Aldo Moro 8, 44124, Ferrara, Italy. E-mail: agnese.suppiej@unife.it

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Abbreviations: JAK2: Janus Kinase 2. CSVT: cerebral sinus venous thrombosis. MTHFR: methylenetetrahydrofolate reductase. MRI: magnetic resonance imaging. MPNs: myeloproliferative neoplasms. CML: chronic myelomonocytic leukemia. PV: polycythemia vera. ET: essential thrombocythemia. PMF: primary myelofibrosis. VKA: vitamin K antagonist.

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Table of Contents Summary*:* This first case of paediatric cerebral sinus venous thrombosis caused by JAK2 V617F mutation, without myeloproliferative neoplasm criteria, expands the thrombosis diagnostic panel for children.

Essential

- Cerebral sinus venous thrombosis (CSVT) is an important cause of vascular accidents in children.

- Risk factors for CSVT in paediatric age are multiple, often co-occurring, modifiable or genetic.
- JAK2 V617F mutation induces thrombogenesis and increases the risk of recurrent thrombosis.
- Molecular study of JAK2 gene should be included in the coagulation panel of children with CVST.

Abstract

Cerebral sinus venous thrombosis (CSVT) is an important cause of vascular accidents in children. The diagnosis of the underlying disease allows appropriate and timely management of the risk factors and guide therapy, but the aetiology remains unknown in 20-25% of the cases. We present the first case of a child presenting CSVT caused by the JAK2 V617F mutation, occurring without the haematological abnormalities diagnostic for myeloproliferative neoplasms. We therefore suggest to include the molecular study of the JAK2 gene in the coagulation panel of all children affected by cerebral sinus venous thrombosis of unknown cause.

Keywords

Pediatric, **Venous Sinus Thrombosis, Myeloproliferative neoplasms, Thrombophilia, Coagulation.**

Cerebral sinus venous thrombosis (CSVT) is a cause of vascular accidents with an estimated incidence of 6-7 per million children under the age of 18[1,2]. Conditions that increase the risk of CSVT in children are infectious processes of the head and neck region, hypercoagulable states and dehydration[3,4]. The diagnosis of the underlying disease allows appropriate and timely management of the modifiable risk factors. This often requires drug administration sometimes for the entire life, with implications for the long-term outcome. Unfortunately, even after thorough investigations, the aetiology remains unknown in 20-25% of the cases, making it difficult to choose the best long-term therapy[3]. Here, we report the case of a girl affected by CSVT where the extensive initial diagnostic work-up could not identify the underlying aetiology. Eventually, the diagnosis was achieved expanding the standard thrombophilia panel test.

CASE REPORT

A 15 years old girl was brought to our department with acute onset of diplopia. In the previous twenty days, she had 3-4 vomits per day, without neurological symptoms, which led to weight loss (4-5 kilograms) due to intentional food and liquids restriction. The blood test (complete blood count, electrolytes, C-Reactive Protein), brain MRI scan without contrast and gastrointestinal endoscopy examinations did not reveal the presence of any health problem. She also performed a routine ophthalmologic evaluation that was normal. Family history revealed that her father died at the age of 33 of heart attack, not further investigated. Concerning the patient's personal history, in

the last 6 years, she has been suffering from migraines with visual aura. Previous coagulation studies, performed in the occasion of menstrual disorders, were normal except for the homozygous A223V mutation in MTHFR (methylenetetrahydrofolate reductase) gene with associated slight hyperhomocysteinemia (22,8 μmol/L range 5,0-15,0 μmol/L); therefore, treatment with folic acid was started. After eighteen days, just after she stopped vomiting, she felt diplopia in the distant vision. The ophthalmologic evaluation showed bilateral papilledema, tortuous and congested retinal vessels, and optic nerve head haemorrhage. Blood tests performed in the paediatric emergency department, including complete blood count, coagulation (prothrombin time, activated partial thromboplastin time, fibrinogen and D-dimer) and infection panel tests, were normal; in particular platelets result 399 x 10^3/μl (normal range: 150-450). Brain MRI with contrast and angio-MRI scans were immediately performed and documented a partial thrombosis of the superior sagittal, right transverse and sigmoid sinuses. Anticoagulation treatment was carried out with low molecular weight heparin for the first 14 days, followed by the addition of warfarin for the next 10 days and then warfarin only. Diplopia resolved within one month and MRI venography improved, even if recanalization was not completed yet, after 1 year from the onset of the disease. Because uncompleted recanalization the patient is still treated with warfarin; cytoreductive therapy is under consideration as a next therapeutic step. All causes of paediatric cerebral CSVT reported in the literature (Table 1) were excluded, including taking estrogen-containing hormonal contraception. The occurrence of hyperhomocysteinemia and dehydration, due to vomiting and liquids restriction with weight loss, were not considered sufficient to explain the pathogenesis of the thrombosis. Because of the recent report of the Janus Kinase 2 (JAK2) V617F mutation found in adult patients affected by CSVT in the absence of diagnostic criteria for myeloproliferative neoplasms (MPNs), we screened for this pathogenic variant as well[5,6,7]. The genetic analysis of JAK2 on our 15 years old patient revealed the presence of the pathogenic mutation V617F (Mut Janus Kinase2 ex14 (V617F) 31.12 %, POS>0.093). Bone marrow biopsy confirmed the diagnosis of Essential Thrombocythemia, despite normal platelet count[8].

DISCUSSION

Here, we report the first paediatric case of cerebral sinus venous thrombosis associated to JAK2 V617F mutation, occurring without haematological abnormalities suggestive of an overt MPN. The final diagnosis was Essential Thrombocythemia.

Due to the great variability in clinical manifestations and vague clinical symptoms, CSVT is extremely difficult to be diagnosed in children based on clinical manifestations alone, making it a relatively under-recognised condition[9,3].

CSVT in paediatric age often results from multiple risk factors for thrombus formation, insufficient in isolation as in case we presented, often co-occurring in the same patient[4]. Many of them are modifiable, while others are genetic[10]. Table 1 summarises the risk factors for CSVT in paediatric age reported in the literature. The most frequently reported risk factors are infectious processes of the head and neck region, hypercoagulable states and dehydration; cancer (especially haematological malignancies) represents an important subgroup. The most frequent genetic thrombophilic risk factors for CSVT reported in children's cohorts are the MTHFR mutation[4] and factor V Leiden[2]. Iram Javed et al. (2018) found a deficiency of protein C, S and antithrombin III in 31% of the patients affected by CSVT. They also reported that 62,5% of their patients had thrombocytosis, but it is not clear if this was associated with infections, the main cause of CSVT in their group of patients (62,5%). In 20-41% of the cases, the cause of the disease could not be identified even after thorough investigations[3,2].

The Janus Kinase 2 (JAK2) V617F mutation (c.1849G>T, p.Val617Phe) is a somatic gain-of-function mutation[7]. Its presence is a major diagnostic criterion for Philadelphia chromosome-negative MPN[5]. This disorder is characterized by extensive proliferation of multipotent myeloid progenitor cells, including chronic myelomonocytic leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)[7]. JAK2 V617F mutant activates JAK-STAT, PI3K/Akt, and ERK1/2 MAPK signaling pathways, leading to abnormal expansion of myeloid cells[7]

JAK2 V617F mutant induces thrombogenesis by different mechanisms: higher haematocrit with high blood viscosity, enhanced platelet-endothelium interactions, platelet-leukocyte aggregates, increased production of proinflammatory cytokines[7].

In the adult population, the presence of JAK2 V617F gene variants was identified in 37.9% of the patients with MPN[7]. Thrombotic events were observed in 30.2% of the patients with the JAK2 V617F mutation, compared with 9.2% of patients who did not have it. The frequency of thrombotic events was significantly higher in patients with the JAK2 V617F mutation than in those without it, suggesting that patients affected by MPN who also carry the JAK2 V617F

mutation are at increased risk for thrombosis[7]. It is noteworthy to mention that in adult patients not exhibiting haematologic criteria for MPN, venous thrombotic complications (especially splanchnic and cerebral thrombosis) may be the only symptom of the disease. In fact, the reported incidence of positivity to the JAK2 V617F mutation in those patients ranges from 12 to 74% in presence of splanchnic vein thrombosis and it is estimated to be around 4% in presence of CSVT[5]. Most importantly, the finding of the JAK2 V617F mutation in patients with CSVT was associated with a recurrence risk of about 30%, supporting the need for a systematic screening[5].

Contrary to adults, JAK2 gene variants have not yet been described in children affected by CSVT or other types of thrombosis, in the absence of haematological abnormalities, suggestive of overt MPN. Therefore, testing for JAK2 gene mutations has not yet been included in studies of thrombophilia in children.

The identification of the JAK2 V617F mutation may have important implications for early diagnosis of MPN as well as for its treatment. In fact, the standard anticoagulation therapy (vitamin K antagonist [VKA] with or without antiplatelet agents or subcutaneous heparin) was ineffective to prevent recurrence of thrombosis in JAK2 V617F mutant-positive adult patients[5]. For these patients, cytoreductive treatment is suggested, in particular when the JAK2 mutation is associated with slightly subnormal leukocyte, haematocrit, or platelet level[5].

Data regarding secondary prevention strategies are not yet available for the group of children with CSVT associated with JAK2 V617F mutation, without overt MPN haematological criteria.

CONCLUSION

The reported case shows, for the first time, that the JAK2 gene can be implicated in paediatric CSVT of children without clinical or laboratory evidence of myeloproliferative disorders. Considering the important implications of this finding for the disease treatment and prognosis, we suggest including the molecular study of the JAK2 gene in the coagulation panel of all children affected by cerebral venous thrombosis of unknown cause.

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Genetic thrombophilia tests
Deficiency of protein C
Deficiency of protein S
Antithrombin III deficiency
Factor V Leiden
Prothrombin G20210A mutation
Increased factor VIII level
Hyperhomocysteinemia
Traumatic head injuries
Female specific risk factors
Pregnancy
Immediate postpartum period
Oral contraceptives
Hormone replacement therapy
Medications
Growth hormone
L-asparaginase
Methotrexate
Steroids
Infections (especially of head and neck)
Otitis
Mastoiditis
Meningitis
Systemic disease
Inflammatory bowel disease
Systemic lupus erythematosus
Antiphospholipid syndrome
Behçet disease
Thyrotoxicosis
Diabetic Ketoacidosis
Sarcoidosis
Wegener granulomatosis

	Nephrotic syndrome
Iatrogenic	
	Jugular venous catheterization
	Neurosurgical intervention
	Lumbar puncture
Miscellaneous	
	Anemia
	Dehydration
	Obesity
	Paroxysmal nocturnal hemoglobinuria
	Dural arteriovenous fistula
	Arteriovenous malformation
	Spontaneous intracranial hypotension
Cancer (especially haematological malignancies)	
	Acute lymphoblastic leukemia (ALL)
	Myeloproliferative neoplasms
Protein loss condition	
	Enteropathy
	Nephropathy
	Liver failure

Table 1: Risk factors for CSVT in children[2-4,6,9,10]