Late-onset chorea in *JAK2*-associated essential thrombocythemia

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Word count

Main text: 906

Figure(s)/Table(s): 0/1

References: 10

Running title

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mdc3.13105

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Key words

Chorea; *JAK2*; *JAK2*^{V617F}; platelets; thrombocythemia

Somatic mutations in *JAK2* are associated with chronic myeloproliferative neoplasms (MPNs), including polycythemia vera, essential thrombocythemia, and primary myelofibrosis (PMF). The most common variant, Val617Phe (*JAK2*^{V617F}), accounts for >95% of polycythemia vera and 50-60% of essential thrombocythemia and PMF cases.[1, 2]

Chorea is a well-described neurological complication of polycythemia vera,[3] encompassing acute-onset occasionally reversible hemichorea and slowly progressive generalized chorea with prominent oromandibular involvement.[3] The former usually has a vascular etiology, secondary to thrombosis, hemorrhage, or hyperviscosity, whereas the latter has a poorly elucidated pathophysiology.[3]

Here, we describe a case of late-onset generalized chorea with prominent oromandibular involvement associated with *JAK2*^{V617F}-positive essential thrombocythemia (rather than polycythemia vera) and speculate on its pathophysiology.

Case report

A 79-year-old white British woman presented with a one-year history of slowly progressive, persistent generalized involuntary movements most prominently affecting her face and jaw. She reported tongue and lip biting causing chewing and swallowing difficulties, which resulted in clinically significant weight loss over the past six months. Ten years before, the patient was diagnosed with *JAK2*^{V617F}-

positive essential thrombocythemia confirmed on bone marrow biopsy. Essential thrombocythemia had successfully been treated with hydroxyurea 500 mg OD since then, but hematological parameters had recently deteriorated. The patient was still taking hydroxyurea when choreic movements appeared. Few months before our assessment she had undergone a bone marrow aspirate and trephine biopsy showing mild dysplastic changes in the erythroid series (which might be related to age and/or chronic treatment with hydroxyurea) but not evidence of transformation or progression to PMF. There was no history of cognitive or behavioral issues nor exposure to antipsychotic drugs. Her family history was unremarkable.

Neurological examination revealed generalized chorea mainly affecting the oromandibular region and hands. Eye movements, muscle strength, sensation, and reflexes were normal. There were no parkinsonian, pyramidal or cerebellar signs (Video). Her Mini Mental State Examination score was 28/30. There was no splenomegaly.

Extensive diagnostic workup for chorea was performed (Table 1). Brain MRI scan showed mild supratentorial small vessel disease and non-specific symmetric T2 and FLAIR hyperintensities within the brainstem. Cervical spine MRI and whole-body PET were unremarkable. Genetic testing for Huntington disease was negative.

After excluding other etiologies, chorea was attributed to *JAK2*^{V617F}-positive essential thrombocythemia. Tetrabenazine 12.5 mg twice daily was initiated with marked improvement. The patient was referred for hematological reassessment.

Discussion

Unlike its well-recognized association with polycythemia vera,[3] chorea has only once previously been linked to essential thrombocythemia.[4] Venkatesan et al. reported a 55-year-old woman with *JAK2*^{V617F}-positive essential thrombocythemia presenting with acute-onset generalized chorea which reversed after hydroxyurea initiation.[4] Our case confirms *JAK2*-related essential thrombocythemia as a treatable cause of late-onset chorea and reveals that chorea may herald deterioration of hematological parameters, as in polycythemia vera.[5] Moreover, it provides further evidence of the association between chorea and *JAK2*^{V617F}.

The pathophysiology of *JAK2*-associated generalized chorea is controversial. Ischemic damage to the neostriatum due to hyperviscosity and venous stasis has been hypothesized as pathomechanism in polycythemia vera-related chorea.[3] Chorea has been reported also in secondary polycythemia and other hyperviscosity syndromes, including leukemia and sick-cell anemia. However, most functional neuroimaging and pathological studies failed to detect different striatal characteristics in polycythemia vera patients with and without chorea.[3] Furthermore, chorea was reported in *JAK2*^{V617F}-positive patients before or in the absence of hematological abnormalities meeting criteria for MPNs,[6, 7] suggesting that blood hyperviscosity alone is not sufficient to explain chorea development.

Cerebrovascular congestion might alter regional concentrations of neurotransmitters. Upregulation of dopamine receptor sensitivity due to reduced levels of cerebral catecholamines and serotonin has been reported.[3, 8] Moreover, enhanced dopamine receptor sensitivity secondary to relative estrogen deficit in postmenopause, may explain the higher frequency of polycythemia vera-related chorea in elderly females (despite polycythemia vera being more prevalent in males).[8] Finally, excess dopamine release

by platelets has been suggested in polycythemia vera-related chorea, which can also be advocated in essential thrombocythemia.[3, 8]

Recently, Betté and Moore speculated that, since *JAK2* is expressed in vivo by striatal progenitor cells, the somatic gain-of-function variant *JAK2*^{V617F} might cause chorea through local inflammation and impaired neurosignaling in the striatum.[7, 9] In other words, the acquisition of *JAK2*^{V617F} by hematopoietic cells could upregulate systemic cytokines with receptors in the striatum, leading to striatal overactivation and ultimately chorea. This mechanism might also contribute to chorea in autoimmune conditions[8] but does not explain why only a small percentage of *JAK2*^{V617F}-positive patients develop chorea.[3] As chorea has mainly been reported in *JAK2*-related MPNs, we speculate that the specific germline *JAK2* haplotype which predisposes to the acquisition of *JAK2*^{V617F} in hematopoietic cells might influence the expression/regulation of (yet undetermined) genetic and/or epigenetic contributors to chorea in striatal cells.[10]

Regarding laboratory findings, our patient's megaloblastic anemia could be explained by long-term treatment with hydroxyurea. Indeed, hydroxyurea acts by causing myelosuppression, finally resulting in anemia with megaloblastosis as well as decrease in platelet and leukocyte counts. The detection of mildly elevated serum ferritin and serum polyclonal gamma globulins was consistent with an inflammatory status possibly secondary to deterioration of the hematological disease. Since the patient's neurological assessment was normal except for chorea and her brain MRI unremarkable with regard to high ferritin level, we did not pursue alternative diagnostic hypotheses. In keeping with the above-mentioned speculation, increased ferritin levels might reflect the upregulation of systemic proinflammatory cytokines which could play a role in striatal hyperactivity and ultimately chorea.

In conclusion, late-onset chorea may be associated with *JAK2*^{V617F}-related essential thrombocythemia and foretell its deterioration. The pathophysiology of chorea in *JAK2*-related MPNs seems multifactorial and requires further elucidation.

Table 1. Laboratory and genetic findings in the patient reported

Investigation	Result	Reference values
Red cell count	**2.67 x 10^{12}/L**	3.95 – 5.15 x 10^{12}/L
Haemoglobin	**91 g/L**	115 – 155 g/L
HCT	**0.293 L/L**	0.33 – 0.45 L/L
MCV	**109.7 fL**	80 – 99 fL
MCH	**34.1 pg**	27.0 – 33.5 pg
MCHC	**311 g/L**	320 – 360 g/L
RDW	**17.4 %**	11.5 – 15.0 %
Platelet count	341 x 10^9/L	150 – 400 x 10^9/L
MPV	10.8 fL	7 – 13 fL
Blood film	**Anisopoikilocytosis**, no acanthocytes	-
White cell count	4.01 x 10^9/L	3.0 – 10.0 x 10^9/L
Neutrophils	2.61 x 10^9/L	2.0 – 7.5 x 10^9/L
Lymphocytes	**0.33 x 10^9/L**	1.2 – 3.65 x 10^9/L
Monocytes	1.0 x 10^9/L	0.2 – 1.0 x 10^9/L
Eosinophils	0.05 x 10^9/L	0.0 – 0.4 x 10^9/L
Basophils	0.02 x 10^9/L	0.0 – 0.1 x 10^9/L
Sodium	138 mmol/L	135 – 145 mmol/L
Potassium	4.5 mmol/L	3.5 – 5.1 mmol/L
Urea	8.2 mmol/L	1.7 – 8.3 mmol/L
Creatinine	**145 umol/L**	49 – 92 umol/L
Estimated GFR	31	-
Glucose	5.1 mmol/L	4.0 – 7.0 mmol/L
Hb1Ac	42 mmol/mol	20 – 42 mmol/mol
Vitamin B12	419 pg/mL	196 – 772 pg/mL
Folate	9.8 ng/mL	2.9 – 26.8 ng/mL
Total protein	82 g/L	63 – 83 g/L
Paraprotein	No paraprotein detected	-
Serum protein electrophoresis	**Polyclonal increase in gamma globulins**	-
Creatine Kinase	36 IU/L	26 – 140 IU/L
Iron	3.8 umol/L	6.6 – 26.0 umol/L
Ferritin	**240 ug/L**	13 – 150 ug/L
TSH	2.01 mIU/L	0.27 – 4.20
Free T4	15.4 pmol/L	12.0 – 22.0
Alpha-fetoprotein	3.1 kIU/L	0 -6 kIU/L
Beta-2-glycoprotein IgM and IgG	Normal	-
ANA screen	Negative	-
ENA screen	Negative	-
Anticardiolipin antibodies IgM and IgG	Normal	-
Anti-dsDNA antibodies	Negative	-
Syphilis antibody testing	Negative	-
Neuronal antibodies Anti-Purkinje cell antibodies Anti-Tr antibodies Anti-White matter (myelin) Anti-Hu antibodies Anti-Yo antibodies Anti-Ri antibodies Anti-Ma-1 antibodies	Negative	-

Anti-Ma-2 antibodies Anti-CV2 (CRMP-5) antibodies Anti-Amphiphysin antibodies Anti-Zic-4 antibodies Anti-Sox 1 antibodies Anti-Tr antibodies DNER antigen Anti-GAD		
IgLON5 antibody	Negative	-
HIV 1-2 antibodies	Not detected	-
Syphilis antibody testing	Negative	-
Genetic testing of *HTT*	Negative	-

Video Legend

Video of the patient showing choreiform movements in the oromandibular region, motor impersistence on tongue protrusion and mild upper and lower limb chorea in the absence of extrapyramidal or cerebellar signs.

Acknowledgements

The authors are grateful to Dr Isacco Ferrarini (University of Verona, Italy) for his kind support in interpreting hematological findings.

Author roles:

1. Research project: A. Conception, B. Organization, C. Execution;
2. Data Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

SKK: 1A, 2A, 2B, 3A

GDL: 2A, 2B, 3A

FM: 2A, 2B, 3A

EM: 2C, 3B

AL: 2C, 3B

KB: 1A, 2C, 3B

Disclosures

Funding Sources and Conflict of Interest:

No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months:

GDL and FM are supported by the European Academy of Neurology (EAN) Research Fellowship 2020. KPB has received grant support from Welcome/MRC, NIHR, Parkinsons's UK and EU Horizon 2020. He receives royalties from publication of the Oxford Specialist Handbook Parkinson's Disease and

Other Movement Disorders (Oxford University Press, 2008), of Marsden's Book of Movement Disorders (Oxford University Press, 2012), and of Case Studies in Movement Disorders–Common and uncommon presentations (Cambridge University Press, 2017). He has received honoraria/personal compensation for participating as consultant/scientific board member from Ipsen, Allergan, Merz and honoraria for speaking at meetings and from Allergan, Ipsen, Merz, Sun Pharma, Teva, UCB Pharmaceuticals and from the American Academy of Neurology and the International Parkinson's Disease and Movement Disorders Society.

Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work. The authors confirm that written consent for video acquisition and publication was obtained.

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