Complications in children and adolescents with Chuvash polycythemia

In the Chuvash form of congenital polycythemia, a homozygous germ-line VHLR200W mutation leads to impaired degradation of the α subunits of the hypoxia inducible transcription factors (HIF-1α and HIF-2α) and augmented hypoxic responses during normoxia including inappropriately elevated erythropoietin levels. Mutated VHLR200W reportedly binds with increased avidity to suppressor of cytokine signaling 1, which hinders Janus kinase (JAK) 2 degradation, leading to erythropoietin-hypersensitive growth of erythroid progenitors. JAK2 inhibitors have been shown to correct complications at age 19 and 24 years (i.e., chest pain with exertion and paroxysmal atrial tachycardia, respectively). Two subjects were 5.3) in patients with familial hemophagocytic lymphohistiocytosis type 5 (FHL-5). Blood. 2010;116(26):6148-6160.


References


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To the editor:

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In the Chuvash form of congenital polycythemia, a homozygous germ-line VHLR200W mutation leads to impaired degradation of the α subunits of the hypoxia inducible transcription factors (HIF-1α and HIF-2α) and augmented hypoxic responses during normoxia including inappropriately elevated erythropoietin levels. Mutated VHLR200W reportedly binds with increased avidity to suppressor of cytokine signaling 1, which hinders Janus kinase (JAK) 2 degradation, leading to erythropoietin-hypersensitive growth of erythroid progenitors. JAK2 inhibitors have been shown to correct complications at age 19 and 24 years (i.e., chest pain with exertion and paroxysmal atrial tachycardia, respectively). Two subjects were

Baseline characteristics of this cohort are summarized in Table 1. The VHLR200W homozygotes (age range of 6-20 years) tended to be older than the VHL wild-type controls (age range of 3-20 years) but the sex distributions were similar. Eight VHLR200W homozygotes had had intermittent phlebotomies, 13 were being treated with aspirin, and 13 were being treated with cinnarizine, an antihistamine and calcium channel blocker used to promote cerebral blood flow. Prominent symptoms at study entry in the VHLR200W homozygotes included headache in 22, lower extremity pain in 15, and dizziness in 13. Frequent physical findings included plethora and a tendency to lower systolic blood pressure. The median hemoglobin concentration was 19.1 g/dL in the VHLR200W homozygotes vs 14.0 g/dL in the controls, and the erythropoietin concentrations were higher in the VHLR200W homozygotes despite the higher hemoglobin concentrations. Headache was reported in 13 (100%) of VHLR200W homozygotes treated with cinnarizine vs 9 (53%) of those not treated (P = .004), and dizziness was a symptom in 6 (46%) of homozygotes treated with cinnarizine vs 5 (29%) of those not treated (P = .3).

Similarly, headache was a symptom in 12 (92%) of VHLR200W homozygotes treated with aspirin vs 10 (59%) in those not treated (P = .09), and dizziness was a symptom in 5 (38%) of homozygotes treated with aspirin vs 6 (35%) of those not treated (P = .6).

We were able to obtain follow-up information for 29 of the VHLR200W homozygotes and all 16 controls in 2014 at a median of 8 years (range 1-9 years) after entry into the registry (Table 1). Nine subjects (31%), 3 of 15 females and 6 of 14 males, and no controls have had complications. In 7 of these subjects, the complications are plausibly related to Chuvash polycythemia. One male died at the age of 17 years from thromboembolism. Two subjects had cardiac complications at age 19 and 24 years (i.e., chest pain with exertion and paroxysmal atrial tachycardia, respectively). Two subjects were found to have benign cysts: 1 investigated for severe headache at age 21 years had a retro-cerebellar arachnoid cyst, and the other had
This report underscores the life-threatening complications and symptoms impairing quality of life that occur in children and adolescents with Chuvash polycythemia. It is possible that other forms of congenital polycythemia due to disordered hypoxia sensing also have similar adverse effects in children and adolescents, but the sporadic nature of these disorders precludes the assessment of their morbidity and mortality. Further research to identify the mechanisms of these complications and symptoms and to develop effective therapy is needed.

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Acknowledgments: This research was supported in part by Incyte Corporation.

Conflict-of-interest disclosure: A.I.S. participated in designing and conducting the study, data analysis and interpretation, identifying study subjects, and writing the manuscript; G.Y.M. participated in designing and conducting the study, data analysis and interpretation, identifying study subjects; L.A.P. participated in study hypothesis and identifying study subjects; M.N. performed the statistical analysis and interpretation, and identified study subjects; J.T.P. and V.R.G. have received travel support from Incyte Corporation.

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