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The prevalence of hereditary hemorrhagic telangiectasia in Juvenile Polyposis syndrome patients with *SMAD4* mutations

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Background

Juvenile Polyposis Syndrome (JPS) is defined by the presence of ≥ 5 colorectal juvenile polyps or any number of juvenile polyps in an individual with a family history of JPS. Genetic alterations including either point mutations or large rearrangements in *BMPR1A* or *SMAD4* are found in 50% of affected individuals. Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant disease diagnosed upon the presence of epistaxis, visceral arteriovenous malformations (AVM) or mucutaneous telangiectasias. HHT is diagnosed when there are ≥ 3 manifestations and is suspected when there are at least 2 manifestations. Most HHT cases are caused by a germline mutation in *ALK1* or *ENG*, members of the TGFβ signaling pathway. Approximately 22% of patients with Juvenile Polyposis Syndrome (JPS) due to a *SMAD4* mutation have been reported to also have HHT [1]. Most prior publications have few patients and no systematic approach to screening, so the true incidence of the combined JPS/HHT syndrome is not known. Our aim was to determine the prevalence of HHT in our patients with JPS with a *SMAD4* mutation including those who underwent systematic screening for AVM's.

Methods

JPS patients were identified from a comprehensive polyposis database using Cologene© software. Families carrying a germline *SMAD4* mutation were studied by screening affected patients for cutaneous telangiectases and with cardiac bubble ECHO, CAT scan chest, or MRI of brain for other AVMs.

Results

Fourteen of 38 JPS families underwent genetic testing. Nine families were identified to have a *SMAD4* mutation. These families include 21 affected relatives, 11 men and 10 women, with a current mean age of 36.3 years (range 4 - 70). Fourteen affected relatives, from 6 families, underwent HHT screening (7 men and 7 women, with a mean age of 35.4 years (range 15-70). Eleven of 14 (79%) had ≥ 3 HHT manifestations and two of 14 (14 %) had at least 2. In addition, 3 of 7 unscreened affected relatives have presented with at least 2 manifestations of HHT. Of the 24 families that have not had genetic testing or HHT screening one affected family member presented with ≥ 3 HHT manifestations, and two had at least 2 manifestations.

Conclusion

Greater than 90% of our patients with JPS due to *SMAD4* mutations had clinically diagnosed or suspected HHT. Genetic testing should be performed in all JPS patients. In addition, systematic HHT screening is recommended for JPS patients with *SMAD4* mutations.

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