Natural History of Central Nervous System Hemangioblastomas in von Hippel-Lindau Disease.

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Introduction

The most common neoplastic manifestations of VHL are central nervous system (CNS) hemangioblastomas, 60-90% of VHL patients develop multiple hemangioblastomas. While hemangioblastomas are benign tumors, they are associated with significant neurologic morbidity and mortality. Despite the frequency and devastating effects of CNS hemangioblastomas in VHL, their natural history and optimal management are not defined. To determine the natural history of CNS hemangioblastomas, to gain insight into factors affecting tumor development/progression, and to improve management, VHL patients and associated hemangioblastomas were prospectively evaluated using clinical, imaging and genetic analyses.

Methods

VHL patients were enrolled in a prospective study designed to define the natural history CNS hemangioblastomas. Prospective serial imaging, laboratory, genetic and clinical data were analyzed.

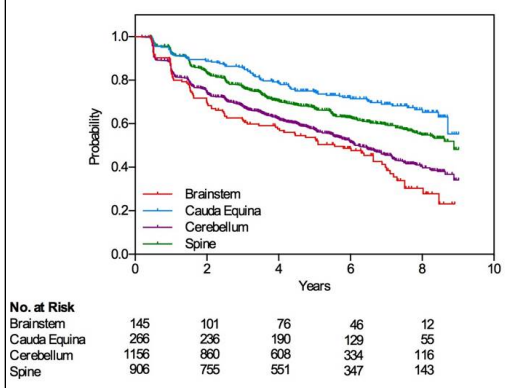
Learning Objectives

By the conclusion of this presentation, participants should be able to: 1) describe the natural history of central nervous system hemangioblastomas, 2) describe the factors that impact tumor development, growth and symptom formation and 3) identify most effective treatment strategies for these neoplasms.

Results

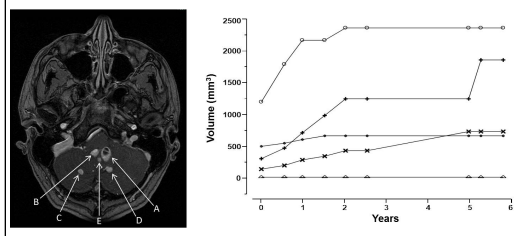
Two hundred twenty-five (111 males; 114 females) patients harbored 1921 CNS hemangioblastomas in the supratentorial compartment (21 tumors; 1%), cerebellum (865; 45%), brainstem (129; 7%), spinal cord (689; 36%), cauda equina (212; 11%) and nerve roots (5; 0.3%) at study entrance (follow-up, 15,819 hemangioblastoma-years). Increased tumor burden was associated with partial deletions in VHL gene (P=0.005) and male sex (P=0.002). Hemangioblastoma development (median, 0.3 new tumors/year) was associated with younger age (P<0.0001) and more tumors at study entrance (P<0.0001). While 1,278 hemangioblastomas (51%) did not grow, 1,226 hemangioblastomas (49%) grew in a saltatory (886 tumors; 72% of growing tumors), linear (76; 6%), or exponential (264; 22%) pattern. Faster tumor growth was associated with male sex (P=0.002), symptomatic tumors (P<0.0001) and tumors associated with cysts (P<0.0001). Location-dependent tumor size was the primary predictor of eventual symptom formation (159 symptomatic tumors [6.4%]; area under the curve greater than 0.9).

Figure 1



Progression of hemangioblastomas at various sites

Figure 2



Characteristic patterns of growth associated with central nervous system hemangioblastomas in von Hippel-Lindau disease patients

Conclusions

CNS hemangioblastoma burden in VHL is associated with partial germline deletions and male sex. Unpredictable growth of hemangioblastomas compromises assessment of non-surgical therapies. Judicious treatment of symptom-producing hemangioblastomas, while avoiding unnecessary treatment of asymptomatic tumors that may not progress, can provide clinical stability.

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