Response to Correspondence "In Pseudotumor cerebri, hormonal contraception is not associated, and the diagnosis remains as 'Idiopathic Intracranial Hypertension'"

REPLY

WE THANK DRS LEE AND FRANCIS FOR THEIR COMMENTS. WE agree that the diagnosis of idiopathic intracranial hypertension (IIH) should be reserved for conditions of intracranial hypertension (ICH) without a known etiology after sufficient investigation.

There are many conditions that can masquerade as IIH, which has been used synonymously with pseudotumor cerebri (PTC) in the literature. As chronicled by Wall and associates (1991), the terminology has evolved since Quincke described the condition in 1897.[1] The term IIH was proposed to convey the expectation that IIH is a diagnosis of exclusion.[2] This requirement is contained within the modified Dandy criteria, which specified that IIH patients must have signs and symptoms of ICH, elevated lumbar puncture opening pressure with normal cerebrospinal fluid constituents, no localizing neurologic finding except cranial nerve VI palsies, normal neuroimaging except for signs of increased intracranial pressure, and no other apparent cause.[3–5] The criteria assume the need for appropriate investigations into possible etiologies of ICH, including a neurologic examination, neuroimaging, a lumbar puncture with measurement of the opening pressure, and analysis of cerebrospinal fluid constituents, before making the diagnosis of IIH.

In the initial survey of IIH patients in our population-based study, the Rochester Epidemiology Project (REP) database was searched for patients with the diagnoses of IIH, intracranial hypertension, PTC, or papilledema.[6] This yielded 427 potential participants, only 63 of whom were confirmed to have IIH after ensuring that they met the modified Dandy criteria. Although we did not specifically screen for all coagulopathies, we excluded 13 patients with cerebral venous sinus thromboses because these patients do not meet the criteria of IIH/PTC. It is possible that some of the prior reported associations between birth control and IIH may have been unrecognized cases of cerebral venous sinus thrombosis because of the known prothrombotic risk of hormonal therapies, which can predispose patients to venous thrombosis.

While there is consensus that a diagnosis of IIH requires the exclusion of known etiologies of ICH, there is debate as to whether IIH should supplant the term "PTC," or represent a subset of PTC, which would also include secondary causes of ICH without an apparent tumor.[2,5] The use of PTC as a synonym of IIH has persisted in the common parlance, with one parenthetically equivalent to the other. Whether the term IIH or PTC is used, we think we can all agree that it is critical to exclude secondary causes of papilledema and ICH, such as tumor or venous sinus thrombosis, before these terms can be applied to patients.

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CONFLICT OF INTEREST DISCLOSURES: SEE THE ORIGINAL article for any disclosures of the authors.

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Are Risk Factors for Growth of Choroidal Nevi Associated With Malignant Transformation? Assessment With a Validated Genomic Biomarker

EDITOR:

WE WOULD LIKE TO COMMENT ON HARBOUR AND ASSOCIates' American Ophthalmological Society thesis "Are risk factors for growth of choroidal nevi associated with malignant transformation? Assessment with a validated genomic biomarker."[1] The authors found that of the many clinical features associated with "malignant transformation" of a melanocytic tumor, only 2, tumor thickness greater than 2.25 mm and patient age (over 60), are significant. There are likely a few exceptions to this, such as

diffuse melanoma. Herein we wish to offer a few additional insights into these important findings.

Thickness likely is a measure of tumor size, and it is known that a larger tumor will generate more mutant cells, including those with the capacity to metastasize.[2] The random mutation rate in uveal melanoma cells for any gene appears rather constant, irrespective of tumor size. The larger (thicker) the tumor, the greater the number of mutated cells, including those capable of intravasating into the vasculature, surviving circulation, and seeding successfully in distant organs, hence the higher the likelihood of clinical metastasis. Two mutations are important for the onset of uveal metastasis. Tumors with *BAP1* mutations display early clinical metastases, while those with *SF3B1* mutations metastasize later.[2] The finding that these 2 types of mutations are most commonly associated with the progression of a uveal nevus into a metastatic melanoma implies that each confers unique and possibly different advantages in the different steps of metastasis that need to be further elucidated.[3]

With regard to patient age, Harbour and associates initially hypothesized that older patients may have more *BAP1* mutations, but found it was not the case.[1] They then proposed that a weakening in the immune microenvironment of the eye may change with age and favor tumor growth. We wish to expand this view and hypothesize that systemic age-related immune changes impact local and distant growth of uveal melanoma. Age alters the functionality of the immune system, a process called "immune senescence" that affects T cells and macrophages.[4] Tumor-immune interactions occur both at the primary tumor site and in invaded organs. Metastatic uveal melanoma cells are found in hematopoietic tissue, including bone marrow[5] and possibly spleen. The expansion of the disseminated cancer cells is constrained by an active immune environment in the liver, the most important end-organ site of uveal melanoma metastasis.[3] Thus the dynamic of tumor-immune cell interactions will likely be modified with age, resulting in lessened antitumor response and increased success of metastatic growth.[4]

Additionally, comprehensive genomic studies by TCGA research consortium have revealed hypoxia signaling as a major transcriptional signature in specific subsets of uveal melanoma at high risk for metastasis.[6] The presence of hypoxia and hypoxia inducible factor 1 (HIF1) signaling in uveal melanoma and the therapeutic value of its targeting have also been recently established.[7] As aging results in decreased blood flow to the choroid,[8] this may accelerate the onset of hypoxia in an emerging tumor, and accelerate tumor vascularization/vasculogenic mimicry,[9] well known risk factors of metastasis. This hypothesis will need to be experimentally assessed in animal models reflecting age-related impediments in blood flow.

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Risk of Stroke After Nonarteritic Anterior Ischemic Optic Neuropathy

EDITOR:

WE ARE INTERESTED TO READ THE STUDY LED BY PARK AND associates[1] about the risk of stroke in patients with nonarteritic anterior ischemic optic neuropathy (NAION). According to this retrospective cohort study, 1125 NAION patients were identified from January 1, 2004 to December 31, 2013, based on the Korean National Health Insurance Service (NHIS)–National Sample Cohort (NSC) database. The occurrence of incident NAION was associated