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Neurofibromatosis Type 2

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Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder characterized by the development of multiple tumors involving the central nervous system (CNS).

Etiology

NF2 is inherited as an autosomal dominant trait in some patients. The abnormal gene can be inherited from either of the parents, and the risk of passing the gene to offspring from a parent is 50%. In some patients with NF2, there is no family history and the disease is caused by a de novo mutation in the *NF2* gene. NF2 is caused by mutations in the *NF2* gene located in the long arm of chromosome number 22 (22q12.2). The *NF2* gene encodes for the protein known as merlin, which acts as a tumor suppressor gene. Merlin is found in the Schwann cells in the nervous system.

Epidemiology

The incidence of NF2 is about 1 in 25,000 to 40,000 individuals.

Pathophysiology

Bilateral vestibular schwannomas are the hallmark feature of NF2 and present in approximately 90% to 95% of patients. Meningiomas are seen in approximately 50% of patients with NF2.

Histopathology

Vestibular schwannomas are benign tumors involving the vestibular portion of the vestibulocochlear nerve (CN VIII). The most common location is an

inferior vestibular nerve. They are well-circumscribed encapsulated tumors arising from the perineural elements of the Schwann cells. They usually cause splaying and displacement of the nerve fibers rather than engagement. Microscopically, two types of cellular architecture can be seen in these tumors: Antoni A and B. Antoni A type regions have dense cellularity with closely packed elongated nuclei alternated with clear zones devoid of nuclei (Verocay bodies). Antoni B type regions are less cellular and contain more loosely arranged cells. The volume of Antoni B regions in any given tumor is variable and may be absent.

History and Physical

NF2 patients typically present with tumor-related symptoms around 20 years of age. The most common intracranial tumor associated with NF2 is vestibular schwannoma which is typically bilateral in these patients. Patients typically present with tinnitus, sensorineural hearing loss and balance problems. The cutaneous features in NF2 are less common and more subtle than NF1. The most common skin finding is an elevated plaque-like lesion which may be hyperpigmented than the surrounding skin. The other cutaneous abnormalities are subcutaneous nodules representing swelling of the nerves and cutaneous tumors which generally represent schwannomas rather than neurofibromas. Patients with meningiomas develop symptoms based on their locations and include a headache, seizures or focal neurological symptoms. NF2 patients tend to develop meningiomas earlier than those with sporadic meningiomas. Approximately 20% of children with meningiomas have NF2. Patients with intraspinal tumors present with pain, muscular weakness and paresthesia.

The clinical diagnosis of NF2 is based on the presence of any one of the following criteria:

- Bilateral vestibular schwannomas less than 70 years of age
- Unilateral vestibular schwannoma before age 70 years and first-degree relative with NF2
- Any two of the following: meningioma, schwannoma (non-vestibular), neurofibroma, glioma, cerebral calcification, cataract *AND* first-degree relative to NF2 *OR* unilateral vestibular schwannoma and negative LZTR1 testing
- Multiple meningiomas and unilateral vestibular schwannoma or any two of the following: schwannoma (non-vestibular), neurofibroma, glioma, cerebral calcification, cataract
- Constitutional or mosaic pathogenic *NF2* gene mutation from the blood or by the identification of an identical mutation from two separate tumors in the same individual.

Evaluation

The detailed clinical history and family history is required from the patients suspected of having NF2. A complete physical examination should be done

to look for cutaneous schwannomas or plaque-like lesions, ophthalmic examination to look for cataracts, optic nerve, among others. Contrast-enhanced MRI of the brain and entire spine is recommended to evaluate schwannomas and meningiomas.

Vestibular schwannoma has characteristic features on the MRI. They are located in the internal auditory canal which is often widened. Large tumors also extend into the cerebellopontine angle and cause the typical "ice cream cone" appearance. These lesions are hypointense on T1-weighted images and hyperintense on T2-weighted images with intense contrast enhancement. Cystic changes can be seen in large tumors. There is a poor correlation between the tumor size and degree of hearing loss.

Meningiomas are the most common extra-axial tumors in the brain. NF2 patients develop meningiomas at an earlier age, and they are often multiple. If meningiomas are seen in the pediatric age group, then a diagnosis of NF2 should be considered. Meningiomas have typical features on the MRI. They are dural-based lesions with the isointense signal on T1-weighted images and iso to the hyperintense signal on T2-weighted images with intense enhancement along with an enhancing dural tail.

Multiple spinal tumors can also be seen in patients with NF2 including schwannomas, meningiomas, and ependymomas and can be diagnosed with MRI. Schwannomas are the most common type; they typically arise from the dorsal root with the typical appearance of dumbbell shape with the widening of the neural foramen and intense enhancement. Meningiomas are enhancing extramedullary lesions, typically seen in the cervical or thoracic region. Ependymomas are intramedullary lesions causing enlargement of the spinal cord with hemorrhage, cystic changes, and variable enhancement.

Treatment / Management

Multidisciplinary management is required in patients with NF2 including oncologists, neurologists, neuroradiologists, ophthalmologists, geneticists, and neurosurgeons. For the tumor surveillance, annual brain MRI is recommended. If there is no brain tumor seen on the initial imaging, then MRI can be done every 2 years. If the tumor is seen, then MRI should be done twice in the first year with annual follow-up after that.

Small asymptomatic vestibular schwannomas can be managed conservatively with MRI follow-up. Surgery is the primary treatment for large symptomatic vestibular schwannomas. Meningiomas are also treated surgically with radiation treatment reserved for non-surgical candidates. The spinal cord ependymomas are usually low-grade tumors and can be followed clinically with surgery reserved for symptomatic patients.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is a new systemic immunotherapy for a wide range of tumors. Some studies have shown tumor regression and hearing improvement in NF2 patients treated with bevacizumab.

Differential Diagnosis

NF2 should be differentiated from Schwannomatosis which is another form of neurofibromatosis, however genetically distinct from both NF1 and NF2. Schwannomatosis is most frequently sporadic with 20% cases being familial. Schwannomatosis is characterized by the development of multiple

schwannomas involving the peripheral nervous system without concomitant involvement of the vestibular nerves. Nonvestibular cranial nerve schwannomas are uncommon but can be seen in these patients.

Questions

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