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Incidental parenchymal magnetic resonance imaging findings in the brains of patients with neurofibromatosis type 2 ☆

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ABSTRACT

Purpose: Whereas T2 hyperintensities known as NF-associated bright spots are well described in patients with neurofibromatosis type I (NF-1), there is a paucity of data on incidental findings in patients with neurofibromatosis type II (NF-2). We aim to characterize unexplained imaging findings in the brains of patients with NF-2.
Materials and methods: This study is retrospective, HIPAA-compliant and approved by the institutional review board. 34 patients with NF-2 underwent brain magnetic resonance imaging (MRI) between January 2000 and December 2012. T2 and T1-weighted imaging characteristics, diffusion weighted imaging (DWI) characteristics, and enhancement patterns were analyzed by visual inspection. Clinical information at time of imaging was available for all patients. Neuropathologic data was available for one patient.
Results: We found unexplained T2 hyperintensities present on initial imaging in 23/34 patients (67%). Of the 23 patients with unexplained MRI findings, 15 (65%) had wedge-shaped T2 hyperintensities in the subcortical white matter extending to the cortex suggestive of a cortical dysplasia. 3 additional cases (17%) had a lesion within the cerebellum suggestive of a neuronal migration anomaly. In one patient where the MRI was suggestive of focal cortical dysplasia, histopathologic analysis revealed dysplastic glial foci without other alterations of cortical architecture or other cytologic abnormalities.
Conclusion: Unexplained T2 hyperintensities occur frequently in patients with NF-2. While they may not be the NF-2 equivalent of NF-associated bright spots seen in NF-1, some of these T2 hyperintensities in patients with NF-2 may represent underlying disorders of neuronal migration. Further studies are needed to validate our findings.

1. Introduction

Neurofibromatosis type II (NF-2) is a neurocutaneous disorder that is caused by genetic mutations of the NF-2 gene on chromosome 22 (Rouleau et al., 1993). The NF-2 gene encodes an intracellular membrane-associated protein, a tumor suppressor known as merlin (Trofatter et al., 1993). Aberrant merlin predisposes individuals with NF-2 to the development of multiple tumors of the central nervous system, including meningiomas, schwannomas and ependymomas (Asthagiri et al., 2009; Hagel et al., 2012). The most common of these tumors are bilateral vestibular schwannomas. Spinal cord tumors are also a prominent component of NF-2.

Hyperintensities on T2-weighted images known as NF-associated bright spots are seen in the brain MRIs of most patients with the other type of neurofibromatosis, neurofibromatosis type I (NF-1) (van Engelen et al., 2008). NF-associated bright spots are focal areas of increased signal intensity that occur most often in the basal ganglia, cerebellum, brainstem, and subcortical white matter. Pathologic studies performed in NF-1 so far have revealed intramyelinic vacuolar changes or spongiotic myelinopathy that correlate with the hyperintensities found on T2-weighted images (DiPaolo et al., 1995). However, there is a lack of data on the existence and significance of unexplained imaging findings in the brains of patients with NF-2. One case report suggests that hyperintensities seen on T2-weighted imaging in the brain of a 21-year-old man with NF-2 were likely due to myelin vacuolization (Sener et al., 2003). This assumption was based primarily on MRI appearance as there was no corresponding histopathology. Furthermore, there are no large-scale pathologic studies on these hyperintensities seen on T2-weighted images in the brains of patients with NF-2.

The purpose of this study was to characterize unexplained T2-hyperintense lesions and other incidental brain MRI findings in patients with NF-2 in an effort to elucidate specific patterns.

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2. Materials and methods

Our retrospective study was approved by our institutional review board, and informed consent was waived. Our study was compliant with the Health Insurance Portability and Accountability Act.

2.1. Study design and patients

We performed a retrospective analysis of brain imaging, histopathology and clinical data on patients with NF-2 to characterize unexplained brain lesions in this population. Patients were included in this study if they had a definitive clinical and/or genetic diagnosis of NF-2 and had brain MRI imaging performed consecutively anytime between January 2000 and December 2012. The lesion inclusion criteria were lesions present on available initial brain MRI and lesions not otherwise explained by tumor, edema, radiation changes or postoperative changes. Brain MRI scans obtained without gadolinium were excluded from the study. Patients who had only one brain MRI available for review were also excluded from the study. Of 37 patients with NF-2 and available imaging during this time period, 34 had two or more brain MRI scans performed. The remaining 3 patients only had spinal imaging available and were excluded from the study. Neuropathologic data was available for one patient who expired during this time period and had complete autopsy performed.

2.2. Image acquisition

All patients were examined with a 1.5-T whole-body MR imaging unit (Echospeed; GE Medical Systems, Milwaukee, Wisconsin) equipped with high-performance gradients and a manufacturer-supplied quadrature head coil. The following conventional sequences were performed: sagittal T1-weighted (300/14 [repetition time in ms/echo time in ms], one signal acquired), transverse T2-weighted fast spin-echo (3000/91, one signal acquired), transverse fast fluid-attenuated inversion-recovery (10,002/172, inversion time of 2.2 s, one signal acquired), transverse T1-weighted (500/14, one signal acquired), and transverse diffusion-weighted echo-planar (6000/99–100, one signal acquired, *b* values of 0 and 1000 s/mm^2) MR imaging. The transverse sequences usually involved the use of a 5-mm section thickness with an intersection gap of 2.5 mm, a 256 × 192 matrix, the same imaging angle along the orbitomeatal line, and a 22- or 24-cm field of view. Gadopentetate dimeglumine (Multi-Hance; Bracco Diagnostics, Princeton, NJ) was administered with each MRI scan to allow for the evaluation of contrast enhancement. Contrast agent administration was performed intravenously in an identical manner with a power injector at a rate of 2 mL/s with a 20-gauge needle unless patient-related factors (e.g., small veins) necessitated the use of a needle with a different size.

2.3. Data interpretation

All images were independently analyzed by visual inspection by an experienced pediatric neuroradiologist (L.A.H.) with 30 years of experience interpreting brain MRI to exclude tumors, vasogenic edema or post-operative changes within the central nervous system (CNS) and to characterize the findings. In addition to T2-weighted imaging characteristics, T1-weighted imaging characteristics, diffusion weighted imaging (DWI) characteristics, and enhancement patterns were analyzed to characterize associated abnormalities. Clinical data at time of all imaging was available for all patients. Spearman's correlation between patient age and number of unexplained lesions was calculated. The histopathologic data was independently analyzed by an experienced neuropathologist (F.R.) with 11 years of experience in interpreting both neoplastic and nonneoplastic neuropathology.

Table 1
Patient demographics.

Number of patients in the study (N)	34
Median age at time of first incidental MRI finding (years)	20
Female, no. (%)	11 (32)
Male, no. (%)	23 (68)
Received cranial irradiation, no. (%)	3 (9)

3. Results

A total of 34 patients were included in this study. 23/34 (68%) were males and 11/34 (32%) were females. The median age at time of unexplained brain MRI finding was 20 years old (range 8–69 years) (Table 1). 23/34 patients (68%) had at least one unexplained finding present on the initial MRI of the brain (Table 2). A total of 73 incidental lesions were identified among the 23 initial patient MRIs. 22/23 patients (96%) had at least one incidental hyperintense finding on T2-weighted imaging. The remaining patient with unexplained abnormal imaging had a purely cortical T1 hypointense and T2 hypointense lesion. The average number of unexplained T2-hyperintensities for all study patients at time of initial brain imaging was 2.2 ± 2.3. The most common location for these T2-hyperintense lesions was the frontal lobe, with a higher frequency appearing in the right frontal lobe. During consecutive brain imaging over a period of at least six months (range up to 12 years), no patient (0%) developed any new unexplained lesions and only two patients were noted to have an increase in incidental lesion size. One patient developed interval increase in the size of his unexplained T2-hyperintense lesion; this patient was among three patients in our study who had received brain radiation. One patient developed an increase in size of a cortical T2 hypointensity (Fig. 1). The remainder of the cases (94%) had no interval change in the size of any of their unexplained lesions. Of the three patients with a history of cranial irradiation, one did not have any unexplained abnormalities on initial or subsequent brain MRI. The other two had incidental findings present on brain MRI prior to the initiation of radiation therapy. The patient with a change in his lesions received conformal radiation therapy with a total of 5400 cGy to the right parietal area for ependymoma completed in December 2007. His unexplained lesions were first noted prior to radiation treatment in May 2007. He developed diffuse white matter T2-hyperintensities in December 2009. A second patient received conformal radiation (dose unknown as performed at an outside institution) to the lower brain stem/upper cervical cord for neurofibroma completed in 1991. His unexplained lesion was first noted in May 2007 and was not observed to change over time. A third patient received conformal radiation (dose unknown as performed at an outside institution) to the right orbit and right skull base for spheno-orbital meningioma completed in April 2004. His unexplained lesions were first noted prior to radiation therapy in May 2002 and were not noted to change over time. Among all 73 incidental lesions, only one was hyperintense on T1-weighted sequences. A total of three unexplained gadolinium-enhancing lesions were identified (4%). Among the three enhancing lesions was leptomeningeal enhancement over a wedge-shaped cortical

Table 2
Results.

Incidental brain MRI finding	Number of patients with finding, no. (%)
Any incidental finding	23 (68)
Nonspecific T2 hyperintensities	17 (74)
Wedge shaped cortical/subcortical T2 hyperintense lesions	15 (65)
Transmantle sign	9 (39)
Cortical T2 hypointensities	8 (34)
Well circumscribed cortical T2 hypointensity with associated T1 hypointensity	6 (26)
Migrational cerebellar anomalies	3 (13)
T2 hyperintense lesions associated with an enlarged Virchow–Robin space	7 (30)
More than one of the above abnormalities	15 (65)