Increased prevalence of brain tumors classified as T2 hyperintensities in neurofibromatosis 1

Jennifer L. Griffith, MD, PhD*, Stephanie M. Morris, MD*, Jasia Mahdi, MD, Manu S. Goyal, MD, Tamara Hershey, PhD, and David H. Gutmann, MD, PhD

Correspondence

Dr. Gutmann
gutmannd@wustl.edu

Neurology: Clinical Practice August 2018 vol. 8 no. 4 283-291 doi:10.1212/CPJ.0000000000000494

Abstract

Background

We sought to define the radiologic features that differentiate neoplastic from non-neoplastic T2 hyperintensities (T2Hs) in neurofibromatosis type 1 (NF1) and identify those lesions most likely to require oncologic surveillance.

Methods

We conducted a single-center retrospective review of all available brain MRIs from 68 children with NF1 ($n = 190$) and 46 healthy pediatric controls ($n = 104$). All T2Hs identified on MRI were characterized based on location, border, shape, degree of T1 hypointensity, and presence of mass effect or contrast enhancement, and subsequently classified using newly established radiologic criteria as either unidentified bright objects (UBOs) or probable tumors. Lesion classification was pathologically confirmed in 10 NF1 cases.

Results

T2Hs were a highly sensitive (94.4%; 95% confidence interval [CI] 86.4%–98.5%) and specific (100.0%; 95% CI 92.3%–100.0%) marker for the diagnosis of NF1. UBOs constituted the majority of T2Hs (82%) and were most frequently located in cerebellar white matter, medial temporal lobe, and thalamus, where they were more likely than probable tumors to be bilateral ($p < 0.001$) and have nondiscrete borders ($p < 0.001$). Surprisingly, 57% of children with T2Hs harbored lesions classified as probable tumors, and 28% of children with probable tumors received treatment. In contrast to UBOs, probable tumors were most frequently located within the globus pallidus and medulla, and rarely occurred prior to 3 years of age.

Conclusions

With the implementation of standardized radiologic criteria, a high prevalence of brain tumors was identified in this at-risk population of children, of which nearly one-third required treatment, emphasizing the need for appropriate oncologic surveillance for patients with NF1 harboring nonoptic pathway brain tumors.

Departments of Neurology (JLG, SMM, JM, DHG) and Radiology (MSG, TH), Washington University School of Medicine, St. Louis, MO.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

*These authors contributed equally to this work.

Of the 335 UBOs detected on at least 2 MRI scans, nearly all remained classified as UBOs on final MRI, with only 6% later reclassified as probable tumor.

The majority of children with neurofibromatosis type 1 (NF1) harbor small focal areas of increased T2-weighted signal (T2 hyperintensities [T2Hs]) on brain MRI.¹ While most of these lesions, colloquially known as unidentified bright objects (UBOs), are thought to represent non-neoplastic abnormalities,² children with NF1 are at substantially increased risk for low-grade brain tumors,^{3,4} which often appear as similar high-signal-intensity foci on T2-weighted imaging.⁵

Low-grade brain tumors are typically characterized by mass effect or contrast enhancement on postgadolinium MRI. However, prolonged relaxation on T1-weighted imaging is a common radiologic feature of low-grade tumors that is frequently not considered when evaluating T2Hs in NF1.⁵ To further complicate the interpretation of neuroimaging results in patients with NF1, one-third of all NF1-associated low-grade brain tumors arise outside of the optic pathway, most commonly in the brainstem and cerebellum—areas where UBOs are also commonly located.^{3,4,6}

Prior studies have employed varying radiographic criteria to differentiate brain tumors from presumed non-neoplastic UBOs. The lack of standardization has made it challenging to reliably interpret neuroimaging studies in patients with NF1, and to determine how best to monitor these MRI abnormalities. Since T2Hs are rarely biopsied or surgically resected,⁶ there is a pressing need for radiologic guidelines that discriminate between UBOs and brain tumors in this at-risk population. To address this unmet need, we employed newly established radiographic criteria to comprehensively characterize these common MRI abnormalities, elucidate the characteristics that differentiate neoplastic from non-neoplastic T2Hs in NF1, and identify those lesions most likely to require further surveillance.

Methods

Study design and participants

All individuals with a clinical diagnosis of NF1, based on NIH diagnostic criteria,⁷ who had a brain MRI performed at

our institution between January 1, 2006, and December 31, 2016 ($n = 170$), were retrospectively identified under an approved human subjects protocol at Washington University. Of those individuals, a subset of patients 21 years or younger were identified for further review ($n = 72$). Four individuals were excluded from analysis due to inadequate or incomplete imaging. Demographic and clinical information, including age, sex, race, family history of NF1, diagnosis of an optic pathway glioma (OPG), diagnosis of a non-OPG tumor, and pathology results when available, and treatment for any tumor was collected from electronic health records. Serial brain MRIs from healthy control patients ($n = 46$) were identified from clinical and research populations ascertained through the Pediatric Diabetes and Pediatric Neurology clinics at St. Louis Children's Hospital (T.H.).

Classification of T2 hyperintensities

All available brain MRIs from both the NF1 ($n = 190$) and control samples ($n = 104$) were obtained using standardized clinical protocols and were independently reviewed by 2 investigators (NF1 sample by J.L.G.; control sample by J.M.). Brain MRIs were excluded from analysis if performed outside of Washington University, if motion or other artifact obscured anatomical regions of interest, or if relevant sequences, including fluid-attenuated inversion recovery (FLAIR), T2-weighted, T1-weighted (T1 spin-echo or magnetization-prepared rapid gradient echo [MPRAGE] sequences), and T1-weighted postcontrast images, were absent. All T2Hs detected on FLAIR and T2-weighted sequences were individually characterized by (1) location, (2) border (discrete vs nondiscrete), (3) shape (round/ovoid, complex/angular, or multilobular), (4) T1 hypointensity (graded as minimal if lesion demonstrated hypointensity on MPRAGE sequences, moderate if lesion demonstrated hypointensity on T1 spin-echo sequences, or marked if lesion was more hypointense than gray matter on any T1-weighted sequence), (5) mass effect (yes or no), and (6) contrast enhancement (graded as faint, heterogeneous, or homogeneous). Consensus regarding the location, borders, and grading of T2H characteristics was

Table 1 Patient demographics

	NF1 group ($n = 68$)	Control group ($n = 46$)	<i>p</i> Value
Age, y (SD) ^a	12.0 (4.1)	13.7 (4.6)	0.04
Sex	34 male (50%)	19 male (41%)	0.36
No. of MRIs (range)	3 (1–6)	3 (1–3)	0.08
Age at first MRI, y (range)	6.3 (0.3–14.8)	12.5 (0.7–20.0)	<0.001
Interval between scans, y (range)	4.5 (0.5–10.3)	2.0 (1–3)	<0.001

Abbreviation: NF1 = neurofibromatosis type 1.

^a As of December 31, 2016.

Figure 1 Typical unidentified bright objects in an individual with neurofibromatosis type 1 (NF1)

reached following training by an experienced neuroradiologist (M.S.G.). Discrepancies or uncertainties about particular lesions were arbitrated by M.S.G., who was blinded to diagnosis and age.

Using previously proposed radiographic criteria, specifically developed as a collaborative effort among 4 tertiary NF referral centers to characterize NF1 brainstem gliomas,³ all T2Hs were classified by likelihood of tumor based on their radiographic characteristics: T2Hs were classified as low likelihood of tumor if they had no associated T1 hypointensity, no mass effect, and no contrast enhancement. Lesions classified as intermediate likelihood of tumor had minimal or moderate T1 hypointensity without mass effect or contrast enhancement, and T2Hs were considered to have a high likelihood of tumor if the lesions were more hypointense than gray matter on any T1-weighted sequence, exhibited mass effect, or exhibited contrast enhancement. In a separate analysis, we found that lesions classified as intermediate likelihood of tumor showed similar characteristics, prevalence, and changes over time as those classified as low likelihood of tumor. Therefore, we refer to all T2Hs with low or intermediate likelihood of tumor as UBOs, and all lesions meeting criteria for high likelihood of tumor as probable tumors.

Statistical analysis

Continuously distributed data adhering to conventional normality assumptions are reported as mean and SD, and were compared using the independent Student *t* test. Categorical variables are reported as frequencies and proportions, and were compared using logistic regression methods. Nonparametric equivalents were employed for non-normally distributed data. With biostatistical support (Michael Wallendorf, PhD, Division of Biostatistics at Washington University), quadratic polynomial random coefficient models were fit for natural log-transformed counts of UBOs and tumors to investigate the change in

UBO and tumor burden with age. Statistical significance was defined as a *p* value of <0.05. All analyses were performed using IBM (Armonk, NY) SPSS, version 23.

Standard protocol approvals, registrations, and patient consents

The Washington University Human Research Protection Office approved this study with waiver of informed consent given the minimal risk associated with the retrospective collection and use of anonymized human subject data.

Table 2 Prevalence of unidentified bright objects (UBOs) based on location

Location	UBO (n = 420), n (%)
Cerebellar white matter	97 (19.3)
Medial temporal lobe	75 (17.9)
Thalamus	67 (15.9)
Globus pallidus	55 (13.1)
Midbrain	31 (7.4)
Pons	23 (5.5)
Periaqueductal region	22 (5.2)
Subcortical white matter	18 (4.3)
Middle cerebellar peduncle	13 (3.1)
Internal capsule	8 (1.9)
Corpus callosum	5 (1.2)
Putamen	3 (0.7)
Medulla	2 (0.5)
Caudate	1 (0.2)
Neocortical gray matter	0 (0.0)

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

A total of 114 individuals were included for analysis: 68 individuals with NF1 and 46 controls. Of the 68 individuals with NF1, 34 (50%) were male and the mean age was 12.0 years (SD 4.1). Seventy-two percent of the NF1 group had more than one MRI available for review (median 3 scans; range 1–6), where the median interval between the first and last MRI scan was 4.5 years

(range 0.5–10.3) and the median age at first MRI scan was 6.3 years (range 0.3–14.8). Of the 46 individuals in the control group, 19 (41%) were male, and the mean age was 13.7 years (SD 4.6). Sixty-three percent of the control group had more than one MRI available for review (median 3 scans; range 1–3), with a median interval between the first and last MRI scan of 2 years (range 1–3), and a median age at first MRI scan of 12.5 years (range 0.7–20.0; table 1).

T2Hs were present in 64 (94%) individuals in the NF1 cohort and none of the control individuals, resulting in 94.4% sensitivity (95% confidence interval [CI] 86.4%–98.5%) and

Figure 2 Evolution of T2 hyperintensities (T2Hs) from initial to final MRI scan

Flowchart depicts the evolution of unidentified bright objects (A) and probable tumors (B) from initial to final MRI, including only those T2Hs that were observed on 2 or more MRI scans. *One lesion resolved after treatment.

100% specificity (95% CI 92.3%–100.0%) for a diagnosis of NF1. Of those individuals in the NF1 cohort who had no observable T2Hs on brain MRI ($n = 4$), one had no identifiable pathologic *NF1* gene mutation, another individual had a novel heterozygous missense variant in the *NF1* gene of unclear clinical significance, and 2 were young at the time of the initial scan (4 months old; 6 years old). Overall, a total of 510 unique T2Hs were identified in the NF1 cohort. Using the radiographic criteria outlined above, 420 (82%) T2Hs were classified as UBOs (figure 1), and all but one individual harbored at least one lesion consistent with a UBO. Although these lesions were identified in all brain regions (except for neocortical gray matter), 57% of all UBOs were localized to the cerebellar white matter, medial temporal lobe, and thalamus (table 2). Compared to probable tumors, UBOs were more likely to occur bilaterally (78.1% vs 44.7%; $p < 0.001$) and were more likely to have nondiscrete borders (94.4% vs 66.7%; $p < 0.001$). When determining classification of a T2H based solely on a FLAIR

or T2-weighted image (e.g., clinical scenario with inadequate MRI sequences to adhere to strict radiographic criteria), lesion border was the only feature on MRI that was predictive of whether a T2H would be classified as a UBO or probable tumor, with UBOs demonstrating a lower likelihood for discrete borders than probable tumors (odds ratio [OR] 0.23; 95% CI 0.08–0.66; $p = 0.006$).

Of the 335 UBOs detected on at least 2 MRI scans, nearly all remained classified as UBOs on final MRI, with only 6% later reclassified as probable tumor (figure 2A). None of these patients became symptomatic or required treatment. Further, no specific features (location, border, shape, laterality, sex, or number of concurrent UBOs) discriminated T2Hs that were later reclassified as probable tumor from those that remained as originally classified. Despite inherent individual variability, fixed effects measures generated from random coefficient modeling of the data suggested that UBO burden increases gradually during early childhood, reaches

Figure 3 Typical gliomas in individuals with neurofibromatosis type 1 (NF1)

(A) Fat-suppressed fluid-attenuated inversion recovery (left) and postcontrast T1 (right) images in a 4-year-old girl with NF1 demonstrate a right medial temporal lobe lesion with circumscribed borders, resulting in architectural distortion/mass effect (solid white arrow). The lesion is also associated with a small focus of enhancement and marked T1 hypointensity (dashed white arrow). This probable tumor was biopsied, revealing a WHO grade I pilocytic astrocytoma with atypical features including an infiltrative growth pattern, increased cellularity, and slightly elevated Ki-67 proliferative index. This child also had a known optic pathway glioma (not shown). (B) T2-weighted (left) and postcontrast T1 (right) images in a 6-year-old girl with NF1 demonstrate a heterogeneous T2-hyperintense left cerebellar mass associated with mass effect (solid white arrow) and contrast enhancement (dashed white arrow). The tumor was subsequently resected and pathology demonstrated a WHO grade I pilocytic astrocytoma with inflammatory cells and microglia, an infiltrative growth pattern, and mildly elevated Ki-67 proliferative index.

a maximum at 6.75 years of age, on average, and then gradually decreases in adolescence (figure e-1, links.lww.com/CPJ/A38).

A total of 90 (18%) T2Hs were classified as probable tumors, where 92% (n = 83) were classified based on the presence of contrast enhancement or mass effect (figure 3). Strikingly, 39 of 68 individuals (57%) had at least one T2H classified as a probable tumor on MRI. While probable tumors were detected in all brain regions, 53% developed in the globus pallidus, midbrain, and medulla (table 3). Of the 50 probable tumors found on at least 2 MRI scans, 24% were later reclassified as UBO on final MRI (figure 2B); however, there were no specific features that discriminated those that were later reclassified from those that were not. Like UBOs, random coefficient modeling of the high-likelihood lesions revealed that tumor burden also tended to increase during early childhood and appeared to peak at approximately 11 years of age (figure e-2, links.lww.com/CPJ/A38). In contrast to UBOs, T2Hs classified as high likelihood for tumor rarely occurred in children younger than 3 years and were significantly less likely than UBOs to resolve with time (25.1% vs 4.0%; $p = 0.001$).

OPGs were identified in 24 individuals (35%) in the NF1 cohort. Although there was no significant difference in the proportion of individuals with probable tumors based on the presence or absence of OPG (67% vs 52%; $p = 0.25$), individuals with OPG had significantly more UBOs than individuals without OPG (7.1 vs 5.6; $p = 0.04$). No differences were observed between male and female participants with

We demonstrate that T2Hs—inclusive of both UBOs and tumors—are present in nearly all individuals with NF1, suggesting that UBOs are a highly sensitive feature of NF1.

respect to number of UBOs, number of tumors, or distribution of T2Hs.

Pathologic analysis and treatment

Ten individuals underwent lesion biopsy—5 were located in the medial temporal lobe, 3 in the cerebellum, 1 in the middle cerebellar peduncle, and 1 in the frontal lobe. All biopsied T2Hs were classified as high likelihood for tumor both at the time of initial MRI and at the time of biopsy—9 of these were classified based on the presence of contrast enhancement or mass effect, and one was classified based on the presence of marked T1 hypointensity alone. All lesions exhibited neoplastic features on pathologic assessment, of which 5 were WHO grade I gliomas, 4 were WHO grade II gliomas, and 1 was a WHO grade IV primitive neuroectodermal tumor (table 4).

All biopsy-proven neoplasms were treated with surgical resection or chemotherapy. While most required only one course of treatment, one WHO grade I glioma (NFT2-Bx-2) required multiple rounds of chemotherapy due to tumor progression, and the high-grade embryonal tumor (NFT2-Bx-7) was surgically resected and aggressively treated with chemotherapy and radiation but was ultimately fatal.

Overall, 12 tumors (10 with biopsy, 2 without) occurring in 11 unique individuals with NF1 were treated with chemotherapy or surgical resection, representing approximately 28% of all individuals with probable tumors (11 of 39). In contrast, no UBOs, regardless of reclassification, required treatment (OR 133.9; 95% CI 7.9–2,285.2; $p < 0.001$).

Discussion

Brain tumors are a significant source of morbidity in children with NF1; however, differentiating nonoptic pathway tumors from non-neoplastic T2H abnormalities on neuroimaging studies continues to represent a major challenge for clinicians who evaluate and manage this at-risk population of individuals. To address this clinically important issue, we utilized uniform radiologic criteria to systematically classify all T2Hs occurring in a single NF1 cohort. This study makes several notable points relevant to the assessment of T2Hs arising in children with NF1.

Table 3 Prevalence of probable tumors based on location

Location	Tumor (n = 90), n (%)
Globus pallidus	25 (27.8)
Midbrain	14 (15.6)
Medulla	9 (10.0)
Cerebellar white matter	7 (7.8)
Pons	7 (7.8)
Middle cerebellar peduncle	7 (7.8)
Medial temporal lobe	6 (6.7)
Thalamus	5 (5.6)
Subcortical white matter	2 (2.2)
Corpus Callosum	2 (2.2)
Internal capsule	2 (2.2)
Periaqueductal region	1 (1.1)
Putamen	1 (1.1)
Caudate	1 (1.1)
Neocortical gray matter	1 (1.1)

Table 4 Characteristics of biopsied lesions

Patient ID	Brain location	Radiographic criteria				Pathology	Treatment
		Marked T1 hypointensity	Contrast enhancement	Mass effect	Likelihood of tumor at biopsy		
NFT2Bx-1	Medial temporal lobe	Y	Y	N	High	WHO grade II glioma	Resection
NFT2Bx-2	Cerebellar white matter	Y	Y	Y	High	WHO grade I glioma	Chemotherapy
NFT2Bx-3	Medial temporal lobe/ cerebellar peduncle	Y	Y	Y	High	WHO grade II glioma	Chemotherapy
NFT2Bx-4	Medial temporal lobe	Y	Y	Y	High	WHO grade I glioma	Partial resection and chemotherapy
NFT2Bx-5	Medial temporal lobe	Y	Y	Y	High	WHO grade I glioma	Resection
NFT2Bx-6	Medial temporal lobe	Y	Y	Y	High	WHO grade II glioma	Resection and chemotherapy
NFT2Bx-7	Frontal lobe	Y	Y	Y	High	WHO grade IV PNET	Resection, chemotherapy, radiation
NFT2Bx-8	Cerebellar white matter	Y	N	N	High	WHO grade II glioma	Resection
NFT2Bx-9	Cerebellum	Y	Y	Y	High	WHO grade I glioma	Resection
NFT2Bx-10	Middle cerebellar peduncle	Y	N	Y	High	WHO grade I glioma	Chemotherapy

Abbreviation: PNET = primitive neuroectodermal tumor.

First, we demonstrate that T2Hs—inclusive of both UBOs and tumors—are present in nearly all individuals with NF1, suggesting that UBOs are a highly sensitive feature of NF1.

This point is underscored by the observation that only 5 of the 68 patients with NF1 (7.3%) lacked UBOs on brain MRI—4 individuals with no T2Hs and 1 individual with only high-likelihood lesions. While T2-hyperintense brain lesions are known to occur in other childhood neurologic disorders, including toxic and metabolic conditions and autoimmune encephalopathies, the MRI abnormalities associated with these conditions are typically widespread, affecting bilateral white and gray matter, and are commonly associated with profound neurologic symptoms.^{8,9} In contrast, the MRI finding of multiple asymptomatic focal T2Hs primarily affecting the basal ganglia, thalami, medial temporal lobes, cerebellar hemispheres, or brainstem appears to be highly specific for the diagnosis of NF1. Given that these highly sensitive and specific MRI findings tend to develop early in life and are one of the most common manifestations of NF1, it has been consistently proposed that the presence of T2Hs on MRI may serve as a second disease-defining feature, especially in the context of a young child with a suspected, but not yet confirmed, diagnosis of NF1 (i.e., positive family history without defining clinical features).^{10–14} Despite their potential clinical utility, it should be emphasized that MRI under sedation in asymptomatic young children with a suspected diagnosis of NF1 is not currently indicated for this purpose.

Second, while T2Hs—as a whole—occurred most frequently in previously described brain locations, such as the brainstem,

cerebellum, basal ganglia, and thalamus,^{15,16} we found that UBOs and probable tumors exhibit different spatial patterns in the brain. Probable tumors were most commonly observed in the brainstem and basal ganglia, whereas UBOs occurred most frequently in the cerebellum, medial temporal lobes, and thalamus. In keeping with 2 previous studies, one of which identified diffuse bilateral hippocampal T2Hs in 80% of patients and one of which observed hippocampal T2Hs in 64% of patients,^{17,18} approximately 60% of individuals with NF1 in our series had identifiable UBOs in the medial temporal lobes. Despite the high propensity for UBOs to develop in the medial temporal lobe and hippocampus, these specific brain regions, which are linked to learning and memory,¹⁹ remain under-recognized as common locations for the development of NF1-associated UBOs.

This is particularly important in light of the high prevalence of neurocognitive deficits in children with NF1,²⁰ and the postulation that non-neoplastic T2Hs (UBOs) may represent potential biomarkers for cognitive and behavioral dysfunction in NF1. While the presence and number of UBOs has been associated with reduced cognitive functioning in some studies,^{21–23} other reports have failed to identify a relationship between UBO burden and cognitive impairment.^{1,24,25} In this regard, numerous past studies have demonstrated a consistent association between the presence of thalamic lesions and reduced intelligence^{24,26,27}; however, other reported deficits such as attentional problems, sensorimotor impairment, and reduced general cognition, which have been associated with UBOs in the cerebellum and globus pallidus, have not been reliably replicated.^{28–30}

The reproducibility of results between studies is hindered by small sample sizes, inconsistent definitions with respect to neuropsychological measures, variable inclusion criteria, and the absence of uniform radiologic criteria for the accurate classification of T2Hs across studies. While all tumors, as defined by the presence of mass effect or contrast enhancement, are typically excluded from association studies investigating UBOs and clinical outcomes in NF1, we found that 7%–8% of probable tumors identified in our series (one of which was pathologically confirmed) were classified on the basis of exhibiting marked T1 hypointensity alone. This suggests that a proportion of probable tumors may be misclassified as UBOs, consequently confounding the interpretation of results aimed at defining the use of UBOs as radiologic biomarkers in the setting of NF1. In this regard, future studies may be better positioned to reveal associations between UBOs and neurocognitive deficits if uniform radiologic criteria that serve to discriminate neoplastic from non-neoplastic lesions are employed, and the analyses are restricted to specific brain regions.

Finally, and perhaps most unexpectedly, 57% of individuals with NF1 harbored a probable tumor. Moreover, nearly one-third of these children required treatment for their nonoptic pathway tumor, suggesting that brain tumors occurring outside of the optic pathway are considerably more frequent and less clinically benign than commonly appreciated.^{15,31,32} While the frequency of nonoptic pathway tumors observed in this retrospective study may be subject to ascertainment bias, the clinical indication for obtaining neuroimaging in the study sample varied considerably and included typical indications such as vision changes, surveillance of known OPGs, headaches, hypotonia, and epilepsy. As such, we suspect that the discrepant frequencies of nonoptic pathway gliomas reported in this and prior similar studies likely reflects the previous misclassification of T2Hs in the absence of standardized radiologic criteria, rather than a product of systematic bias in this study.

As a validation of the proposed radiologic criteria, all 10 pathologically confirmed neoplasms were correctly classified as probable tumors on initial MRI. While brain biopsy of an asymptomatic low/intermediate-likelihood lesion would not be ethical or clinically indicated, the finding that few probable tumors spontaneously resolved (2/50 patients; 4%) and a significant number of these patients required treatment (>100-fold OR) highlights the need to adopt uniform radiologic criteria to classify NF1-associated T2Hs. Taken together, it is recommended that neuroimaging surveillance be implemented for T2Hs classified as high likelihood for tumor, even in the absence of mass effect or contrast enhancement. Future prospective studies will be required to more completely define the natural history and growth trajectory of nonoptic pathway tumors, as well as to establish consensus guidelines for the routine surveillance of these tumors.

Author contributions

All authors contributed equally to the conceptualization and design of the study. Data were collected by J.L.G., J.M., and

T.H., analyzed by J.L.G. and S.M.M., and interpreted by J.L.G., S.M.M., J.M., M.S.G., and D.H.G. J.L.G., S.M.M., M.S.G., and D.H.G. created the figures. S.M.M. wrote the first draft of the manuscript, and all authors critically contributed to the preparation of the manuscript and approved it for submission.

Acknowledgment

The authors thank Robert C. McKinstry, MD, PhD, Department of Radiology at Washington University, for input during the establishment of the radiologic classification criteria used in this study; and Michael Wallendorf, PhD, Division of Biostatistics at Washington University, for statistical support with generating quadratic polynomial random coefficient models (Eunice Kennedy Shriver National Institute of Child Health & Human Development of the NIH under award U54 HD087011 to the Intellectual and Developmental Disabilities Research Center at Washington University).

Study funding

This study was partially supported by an unrestricted gift from Schnuck Markets, Inc. (Dr. Gutmann) and the Neurologic Sciences Academic Development Award at Washington University School of Medicine under award K12 NS001690 (Dr. Morris).

Disclosure

J.L. Griffith reports no disclosures. S.M. Morris receives research support from NIH. J. Mahdi reports no disclosures. M.S. Goyal has received funding for travel and/or speaker honoraria from Bill and Melinda Gates Foundation and Yakult Bio-sciences Foundation and has participated in medicolegal cases. T. Hershey has received funding for travel and/or speaker honoraria from Pediatric Endocrine Society, Endocrine Society, International Wolfram Association, University of Alabama, and University of Pittsburgh; serves on the editorial board of *Scientific Reports: Neuroscience*; receives research support from NIH; and her spouse is author on patent re: novel formulation of drug and application and receives research support from Sage Pharmaceuticals and NIH. D.H. Gutmann is author on patents re: NF1 gene and protein; receives research support from US Department of Defense, NIH/NCI, The Giorgio Foundation, NF1-Dermal Neurofibroma Consortium, Children's Tumor Foundation, and Neurofibromatosis Therapeutics Acceleration Program; receives license fee payments for technology re:TSC1 knockout mouse; and receives royalty payments from University of Michigan for NF1 gene patent. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Received March 1, 2018. Accepted in final form April 18, 2018.

References

1. Ferner RE, Chaudhuri R, Bingham J, Cox T, Hughes RA. MRI in neurofibromatosis 1: the nature and evolution of increased intensity T2 weighted lesions and their relationship to intellectual impairment. *J Neurol Neurosurg Psychiatry* 1993;56:492–495.

2. DiPaolo DP, Zimmerman RA, Rorke LB, Zackai EH, Bilaniuk LT, Yachnis AT. Neurofibromatosis type 1: pathologic substrate of high-signal-intensity foci in the brain. *Radiology* 1995;195:721–724.
3. Mahdi J, Shah AC, Sato A, et al. A multi-institutional study of brainstem gliomas in children with neurofibromatosis type 1. *Neurology* 2017;88:1584–1589.
4. Rodriguez EJ, Perry A, Gutmann DH, et al. Gliomas in neurofibromatosis type 1: a clinicopathologic study of 100 patients. *J Neuropathol Exp Neurol* 2008;67:240–249.
5. Forst DA, Nahed BV, Leoffler JS, Batchelor TT. Low-grade gliomas. *Oncologist* 2014;19:403–413.
6. Helfferich J, Nijmeijer R, Brouwer OF, et al. Neurofibromatosis type 1 associated low grade gliomas: a comparison with sporadic low grade gliomas. *Crit Rev Oncol Hematol* 2016;104:30–41.
7. National Institutes of Health consensus development conference statement: neurofibromatosis. *Arch Neurol* 1988;45:575–578.
8. Sharma P, Eesa M, Scott JN. Toxic and acquired metabolic encephalopathies: MRI appearance. *AJR Am J Roentgenol* 2009;193:879–886.
9. Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B. Autoimmune encephalitis: pathophysiology and imaging review of an overlooked diagnosis. *AJNR Am J Neuroradiol* 2017;38:1070–1078.
10. Lubs ML, Bauer MS, Formas ME, Djokic B. Lisch nodules in neurofibromatosis type 1. *N Engl J Med* 1991;324:1264–1266.
11. Gutmann DH, Aylsworth A, Carey KC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997;278:51–57.
12. DeBella K, Poskitt K, Szudek J, Friedman JM. Use of “unidentified bright objects” on MRI for diagnosis of neurofibromatosis 1 in children. *Neurology* 2000;54:1646–1651.
13. Lopes FFJR, Munis MP, Soares SA, et al. Unidentified bright objects on brain MRI in children as a diagnostic criterion for neurofibromatosis type 1. *Pediatr Radiol* 2008;38:305–310.
14. Sabol Z, Resic B, Juraski RG, et al. Clinical sensitivity and specificity of multiple T2-hyperintensities on brain magnetic resonance imaging in diagnosis of neurofibromatosis type 1 in children: diagnostic accuracy study. *Croat Med J* 2011;52:488–496.
15. Menor F, Marti-Bonmati L, Arana E, Poyatos C, Cortina H. Neurofibromatosis type 1 in children: MR imaging and follow-up studies of central nervous system findings. *Eur J Radiol* 1998;26:121–131.
16. Rosenbaum T, Engelbrecht V, Krolls W, Van Dorsten FA, Hoehn-Berlage M, Lenard HG. MRI abnormalities in neurofibromatosis type 1 (NF1): a study of men and mice. *Brain Dev* 1999;21:268–273.
17. Yamanouchi H, Kato T, Matsuda H, Takashima S, Sakuragawa N, Arima M. MRI in neurofibromatosis type 1: using fluid-attenuated inversion recovery pulse sequences. *Pediatr Neurol* 1995;12:286–290.
18. Gill DS, Hyman SL, Steinberg A, North KN. Age-related findings on MRI in neurofibromatosis type 1. *Pediatr Radiol* 2006;36:1048–1056.
19. Brown TI, Stern CE. Contributions of medial temporal lobe and striatal memory systems in learning and retrieving overlapping spatial memories. *Cereb Cortex* 2014;24:1906–1922.
20. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. *Dev Med Child Neurol* 2013;55:111–125.
21. North K, Joy P, Yuille D, et al. Specific learning disability in children with neurofibromatosis type 1: significance of MRI abnormalities. *Neurology* 1994;44:878–883.
22. Feldmann R, Denecke J, Grenzebach M, Schuierer G, Weglage J. Neurofibromatosis type 1: motor and cognitive function and T2-weighted MRI hyperintensities. *Neurology* 2003;61:1725–1728.
23. Denckla MB, Hofman K, Mazzocco MM, et al. Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis-1. *Am J Med Genet* 1996;67:98–102.
24. Goh WH, Kohn PL, Leung CSY, Wong VC. T2-weighted hyperintensities (unidentified bright objects) in children with neurofibromatosis 1: their impact on cognitive function. *J Child Neurol* 2004;19:853–858.
25. Hyman SL, Gill DS, Shores EA, Steinberg A, North KN. T2 hyperintensities in children with neurofibromatosis type 1 and their relationship to cognitive functioning. *J Neurol Neurosurg Psychiatry* 2007;78:1088–1091.
26. Hyman SL, Gill DS, Shores EA, et al. Natural history of cognitive deficits and their relationship to MRI T2-hyperintensities in NF1. *Neurology* 2003;60:1139–1145.
27. Feldmann R, Schuierer G, Wessel A, Neveling N, Weglage J. Developmental of MRI T2 hyperintensities and cognitive functioning in patients with neurofibromatosis type 1. *Acta Paediatr* 2010;99:1657–1660.
28. Chabernaud C, Sirinelli D, Barbier C, et al. Thalamo-striatal T2-weighted hyperintensities (unidentified bright objects) correlate with cognitive impairments in neurofibromatosis type 1 during childhood. *Dev Neuropsychol* 2009;34:736–748.
29. Moore BD, Slopis JM, Schomer D, Jackson EF, Levy BM. Neuropsychological significance of areas of high signal intensity on brain MRIs of children with neurofibromatosis. *Neurology* 1996;46:1660–1668.
30. Piscitelli O, Digilio MC, Capolino R, Longo D, Di Ciommo V. Neurofibromatosis type 1 and cerebellar T2-hyperintensities: the relationship between cognitive functioning. *Dev Med Child Neurol* 2012;54:49–51.
31. Sellmer L, Farschtschi S, Marangoni M, et al. Non-optic glioma in adults and children with neurofibromatosis 1. *Orphanet J Rare Dis* 2017;12:34.
32. McGaughan JM, Harris DI, Donnai D, et al. A clinical study of type 1 neurofibromatosis in north west England. *J Med Genet* 1999;36:197–203.

Practice Current: An interactive exchange on controversial topics

Share your own best practices.

Read commentary with expert opinion.

Explore results on an interactive world map.

NPub.org/NCP/practicelcurrent

Neurology® Clinical Practice