Original Article

Globus pallidus high-signal lesions: A predominant MRI finding in children with neurofibromatosis type 1

Arif Khan, Sushil Beri[1], Aravindhan Baheerathan, Anand Balki, Nahin Hussain, Jayprakash Gosalakkal

Departments of Pediatric Neurology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, [1]Paediatric Neurology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

Abstract

Introduction: Lesions of the brain, recognized as unidentified bright objects (UBOs), are commonly observed as areas of increased T2-weighted signal intensity on magnetic resonance imaging (MRI) in children with neurofibromatosis type 1 (NF1). Identification of these lesions is not currently encompassed in the National Institute of Health (NIH) diagnostic criteria for NF1. **Objective:** We aimed to determine the prevalence of UBOs in children with NF1 and identify areas of the brain that are commonly affected by these lesions, allowing us to evaluate whether UBOs should be included in the diagnostic criteria for the diagnosis of NF1. **Materials and Methods:** We reviewed the cranial MRI scans of 22 children who had been diagnosed with sporadic or familial NF1 in accordance with the criteria established by NIH. UBOs were present in 81% of the children with NF1. **Results:** These lesions have a predilection for specific areas of the brain, including the globus pallidus (72%), cerebellum (66%), brainstem (27%) and cerebral hemispheres (16%). The prevalence of UBOs identified varied significantly with age and sex; they were infrequent in children less than 4 years of age but were common in those aged between 4 and 12 years of age. UBOs were more commonly seen in males (66.6%) compared with females (33.3%). Repeat MRI scan on a subset of these patients with UBOs did not show any significant changes despite a worsening in clinical symptoms. **Conclusion and Discussion:** We have shown that UBOs are a common finding in children with NF1, and are most prevalent between the ages of 4 and 12 years. Many sites of the brain are affected by these lesions, most notably the globus pallidus and the cerebellum. Further research must be conducted to elucidate the significance of UBOs in patients with NF1 and whether these lesions have any utility in the clinical detection of NF1.

Key Words

Globus pallidus, magnetic resonance imaging, neurofibromatosis type 1, unidentified bright objects

For correspondence:

Dr. Arif Khan, Department of Pediatric Neurology, Leicester Royal Infirmary, Infirmary Square, Leicester, United Kingdom.
E-mail: khangoa@hotmail.com

*Ann Indian Acad Neurol 2013;16:000-000****

Introduction

Neurofibromatosis type 1 (NF1) is transmitted as an autosomal-dominant trait, and is noted for its variable expression.[1] It is a disorder that primarily affects the nervous systems and the skin; however, it can also have manifestations upon the musculoskeletal, endocrine, gastrointestinal and vascular systems.[2] The estimated prevalence is one in 4000.[3] The NF1 gene is located at 17q11.2 and encodes a 2818-amino acid protein referred to as neurofibromin.[4] It is characterized clinically by café-au-lait spots, freckling, lisch nodules, neurofibromas, optic gliomas and bone lesions.[5] NF1 is diagnosed by using a set of clinical criteria that was developed by the National Institute of Health (NIH) in 1988[6]; however, NF1 remains a challenging disorder to diagnose, particularly in the pediatric age group.

Unidentified bright objects (UBOs) are specific lesions in the brain that are commonly seen on magnetic resonance imaging (MRI) of patients with NF1. These are areas of increased T2-weighted signal intensity and show no mass effect or contrast enhancement.[7,8] Considered to be benign hamartomas, UBOs are present in 43–93% of children with NF1 and are characteristically absent in the first 2 years.[9-12] They increase in number and size until 12 years of age and are rarely seen in patients older than 20 years of age.[13,14] Pathologically, they correspond to areas of vacuolar or spongiotic change in the brain substance.[15] UBOs are not currently considered as a part of the diagnostic criteria for NF1 despite being commonly observed in young NF1 patients.[10,11] In our study, we evaluated the prevalence of UBOs in different age groups, while also assessing their anatomical distribution and variation with respect to the sex of the patient.

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: ***

NF1 is a difficult disorder to diagnose in pediatric patients due to the paucity of clinical signs in the first few years of life; thus, due to the common occurrence of UBOs in this patient group, we propose the inclusion of UBOs as a diagnostic criterion in NF1 patients.

Materials and Methods

This was a retrospective study that comprised of all the patients diagnosed with NF1 using the NIH criteria in our hospital over the last 10 years. The study population comprised of 22 children between the ages of 2 and 16 years.

The MRI scans of all 22 patients were reviewed by an experienced neuroradiologist who reported on the presence of UBOs, their location, mass effect, contrast enhancement and restriction on diffusion-weighted images. We analyzed the frequency of UBOs and their age and sex distribution, and also assessed which parts of the brain were commonly affected by these lesions. We also reviewed the course of UBOs in a subset of patients who had follow-up MRI scans requested based on progression/deterioration of their clinical symptoms.

Results

The cranial MRI scans of 22 children with NF1 were analyzed. UBOs were seen in 18 (81.8%) children of the sample population. The number of UBOs identified varied significantly with respect to the age and sex of the patient. They were uncommon in children less than 4 years, but were frequent found (100%) in the 4-12 years group. The mean age of presentation was 8 years, and a significant reduction in number was demonstrated in children older than 14 years [Table 1].

Of the children identified with UBOs, 66.6% were males and 33.3% were females.

UBOs were found to be distributed in various anatomical sites of the brain; the globus pallidus was the region most frequently associated with UBOs (72.2%). Other affected areas included the cerebellum (66.6%), brainstem (27.7%) and cerebral hemispheres (16.6) [Figures 1 and 2].

Among the 18 children with UBOs, seven had follow-up MRI scans; these were performed to rule out the development of intracranial tumors as patients had complained of clinical deterioration (headaches and vomiting). Five children showed no significant changes in the size and location of the lesions, one developed a new frontal lobe lesion and the other developed an increase in size of the UBO situated in their corpus callosum. We found that none of the children demonstrated any clinical features attributable to the regions that had been affected by the UBOs.

Table 1: The frequency of UBOs in the different age groups

Categories of patients	Total numbers	With UBOs	(%)
Study group	22	18	81
0–4 years	2	0	0
4–12 years	11	11	100
12–16 years	9	7	77

UBOs = Unidentified bright objects

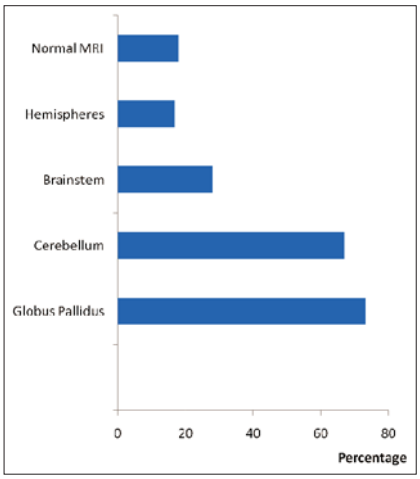

Figure 1: The distribution of unidentified bright objects in the brain and the sites that are commonly affected by these lesions

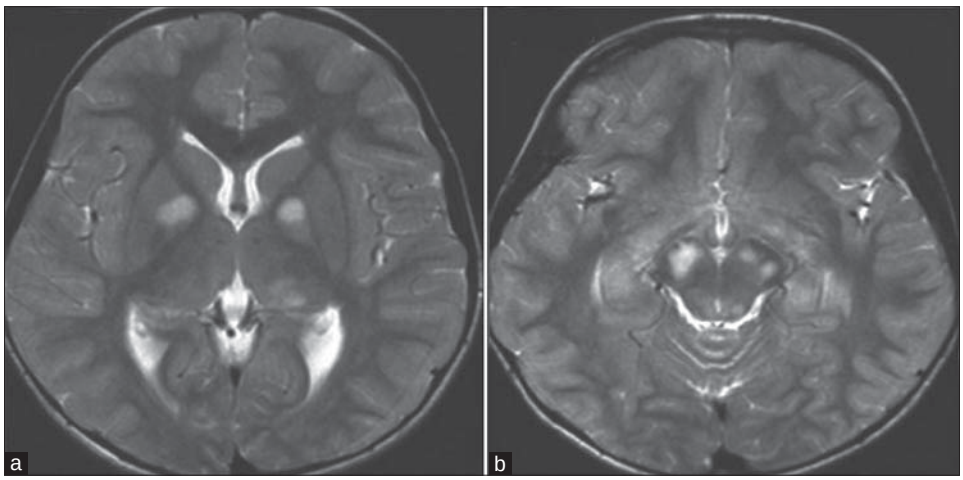

Figure 2: Magnetic resonance imaging of the brain showing T2 hyperintensity signals involving (a) globus pallidus and (b) brain stem

Discussion

NF1 was described clinically and scientifically in the late 1800s by Friedrich Danial von Recklinghausen and was localized to chromosome 17 in 1990.[16-18] It is an autosomal-dominant disorder with an incidence of approximately one in 4000.[3] The most reliable approach to the diagnosis of NF1 remains an assessment of clinical features. The diagnostic criteria of NF1 are based on consensus statement developed by the NIH in 1988 and reaffirmed in 1997.[6,19]

UBOs are areas of hyperintense signal on T2-weighted images, and these are more conspicuous on fluid-attenuated inversion recovery MRI sequences (FLAIR). They are observed in the brain of most children with NF1, and they tend to evolve over time.[20,21] There have been several reports in the literature that postulate the exact nature of these lesions. Histopathological reports suggest that these lesions are characterized by spongiform myelinopathy or vacuolar changes of myelin filled with water, explaining why these lesions are bright on T2-weighted images.[22] The abnormal myelin development may be a result of delayed glial differentiation[23] or chemical abnormality.[15,23] This is however replaced by more chemically normal myelin or there is regression of intramyelinic edema,[22] suggesting a decrease in incidence with advancing age.[15,22]

In our study, UBOs were identified in 100% of the children with NF1 aged between 4 and 12 years. It also demonstrated a lower frequency (72%) of UBOs in older NF1 patents; thus, correlating with previous reports and hypotheses that suggest regression of these lesions during adolescence.[21,24,25]

UBOs were most frequently found in the globus pallidus [Figure 2]; a finding that correlated with other studies on this subject matter.[21,23-25] Other commonly affected areas were the cerebellum, brainstem and cerebral hemispheres. Of the subgroup who had a repeat MRI scan, 71% showed no significant changes, while one had a new frontal lobe lesion and the other had an increase in the size of the existing lesion. However, the association between worsening clinical features and an increase in the size/number of the UBOs remains ambiguous. It is also important to acknowledge that none of these abnormalities showed any mass effect, contrary to the study by Griffiths *et al*., who in their study of 46 children showed that five children developed tumors in the region of previously recognized UBOs and demonstrated mass effect with enhancement after gadolinium-DTPA.[21]

Earlier studies by Goh *et al*. had shown low attention scores in children with hyperintensities involving the globus pallidus.[9] Our study group did not replicate these findings and did not show any clinical features attributable to the involvement of the affected regions. It is likely that the clinical manifestation of UBOs depends on the region involved, as studied by Moore *et al*., who showed that hyperintensities in the cerebral hemispheres, basal ganglia, brainstem or cerebellum had no impact on neuropsychological functioning, whereas such lesions in the thalamus were associated with greater intellectual and neuropsychological impairment.[26]

Conclusion

Our overall results reaffirm findings from previous studies that report the involvement of UBOs in the globus pallidus, cerebellum and brainstem in children with NF1. We have also shown that UBOs are common during the early years of childhood and are rarely seen in older children. Most UBOs follow a benign course, although only a small proportion of children had repeat MRI scans, as per the recommendations put forward by the Committee on Genetics of the American Academy of Pediatrics;[27] the majority of this subset had no significant changes. None of the children in the study group had any clinical symptoms attributable to the lesions in the different areas of the brain. Further research must be conducted to elucidate the significance of UBOs in patients with NF-1 and whether these lesions have any utility in the clinical detection of NF1.

References

1. Lobo I. Same genetic mutation, different genetic disease phenotype. Nature Education 2008;1. Retrieved from http://www.nature.com/scitable/topicpage/same-geneticmutation-different-genetic-disease-phenotype-938.
2. Elizabeth AT, Bruce RK. Genetic, metabolic and neurocutaneous disorders. Paediatric Neurology. Vol 1, 4th ed. 772-4.
3. North K. Neurofibromatosis type 1. Am J Med Genet 2000;97:119-27.
4. Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type 1 (NF1). J Med Genet 1996;33:2-17.
5. Williams VC, Lucas J, Babcock MA, Guttman DH, Korf B, Maria BL. Neurofibromatosis type 1 revisited. Pediatrics 2009;123:124-33.
6. Stumpf DA, Alksne JF, Annegers JF. Neurofibromatosis. Arch Neurol 1988;45:575-5787. Aoki S, Barkovich AJ, Nishimara K, Kjos BO, Machida T, Cogen P, *et al*. Neurofibromatosis type 1 and 2: Cranial MR findings. Radiology 1989;272:527-34.
8. Truhan AP, Filipek PA. Magnetic resonance imaging: Its role in the neuroradiologic evaluation of NF, tuberous sclerosis and sturge-weber syn. Arch Dermatol 1993;129:219-26.
9. Goh WH, Khong PL, Leung CS, Wong VC. T2 weighted hyperintensities (UBO) in children with NF1: Their impact on cognitive function. J Child Neurol 2004;198:853-8.
10. Gill DS, Hyman SI, Stenberg A. Age related findings on MRI in NF type 1. Pediatr Radiol 2006;31:1048-56.
11. Debella K, Poskit K, Szudek J, Friedman M. Use of unidentified bright objects on MRI for diagnosis of NF1 in children. Neurology 2000;54:1646-51.
12. Kim BS, Elles J, Kaplan RT, Reiss A, Atlas AW. Incidental finding on pediatric MR images of the brain. AJNR Am J Neuroradiol 2002;23:1674-7.
13. Togini G, Ferrozzi F, Garlaschi G. Brain apparent diffusion coefficient evaluation in pediatric patients with NF type1. J Comput Assist Tomogr 2005;29:298-304.
14. Hyman SI, Gill DS, Shores EA, Steinberg A, Joy P, Gibikote SV, *et al*. Natural history of cognitive deficits and their relationship to MRI T2 hyperintensities in NF1. Neurology 2003;60:1139-45.
15. Sevick RJ, Barkovich AJ, Edwards MS, Koch T, Berg B, Lempert T. Evolution of white matter lesions in NF type 1: MR findings. AJR Am J Roentgenol 1992;159:171-5.
16. Crump T. Translation of case reports on multiple fibromas of the skin and their relationship to multiple neuromas by F. V. Recklighausen, V. M. Riccards. YJBM.1981;23: 259-75.
17. Viskochil D, Buchberg AM, Xu G, Cawthon RM, Stevens J, Wolff RK. Deletion and a translocation interrupt a closed gene at neurofibromatosis type 1 locus. Cell 1990;62:187-92.
18. Wallace MR, Marchuk DA, Anderson LB, Letcher R, Odeh HM, Saulino AM. Type 1 neurofibromatosis gene: Identification

of a large transcript disrupted in three NF1 patients. Science 1990;249:181-6.
19. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE. The diagnostic evaluation and multidisciplinary management of NF1 and NF2. J Am Med Assoc 1997;278:51-7.
20. Bognanno JR, Edwards MK, Lee TA, Dunn DW, Roos KL, Klatte EC. Cranial MR imaging in neurofibromatosis. AJR Am J Roentgenol 1988;151:381-8.
21. Griffiths PD, Blaser S, Mukonoweshuro W, Armstrong D, Milo-Mason G, Cheung S. Neurofibromatosis bright objects in children with NF1: A proliferative potential. Pediatrics 1999;104:e49.
22. Dipaolo DP, Zimmerman RA, Rorke BL, Zackai EH, Bilaniuk LT, Yachnis AT. NF1: Pathological substrate on high-signal intensity foci in the brain. Radiology 1995;195:721-4.
23. Itoh T, Magnaldi S, White RM, Denckla MB, Hovman K, Naidu S. NF type 1: The evolution of deep grey and white matter abnormalities. AJNR Am J Neuroradiol 1994;15:1513-9.
24. DiMario FJ, Ramsby G. Magnetic resonance imaging lesion analysis in NF type 1. Arch Neurol 1998;55:500-5.
25. Filho JR, Munis MP, Souza AS. Unidentified bright objects on brain MRI in children as a diagnostic criterion for NF type 1. Pediatr Radiol 2008;38:305-10.
26. Moore BD, Slopis JM, Schemer D. Neuropsychological significance of areas of high signal intensity on brain MRI of children with NF. Neurology 1996;46:1660-8.
27. Committee on genetics health supervision for children with Neurofibromatosis. Pediatrics 1995;96:368-72.

How to cite this article: ???

Received: 25-02-12, **Revised:** 15-04-12, **Accepted:** 16-04-12

Source of Support: Nil, **Conflict of Interest:** Nil

Author Queries???

AQ1: Reference not found in PubMed. Kindly provide journal abbreviation and page range.

AQ2: Kindly check this reference.

AQ3: Reference not found in PubMed. Kindly provide Journal abbreviation.