Neurofibromatosis Bright Objects in Children With Neurofibromatosis Type 1: A Proliferative Potential?

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ABSTRACT. Objectives. The purpose of this study was to investigate the natural history of the high signal intensities shown on long TR sequences—neurofibromatosis type 1 bright objects (NBO)—in children with neurofibromatosis type 1 (NF1). We have paid particular attention to the development of tumors in these areas of abnormality.

Methods. During a 12-month period in 1992 to 1993, 46 children with clinically proven NF1 had a magnetic resonance (MR) examination at our institution. These were reviewed along with any previous or subsequent MR examinations that had been performed. We recorded the number, volume, and distribution of the abnormal high signal intensities and their change with time when serial examinations were performed.

Results. NBO were found in 93% of 46 children with NF1 on the original cross-sectional study. The most common anatomic sites were the globus pallidus (30.4%), cerebellum (23.5%), and midbrain (16.2%). The number and volume of NBO varied significantly with age. NBO were uncommon in children younger than 4 years but were very common and extensive between 4 to 10 years. A significant reduction in the number and volume of NBO was demonstrated in children older than 10 years as shown on both the cross-sectional and longitudinal portions of the study. Eight brain tumors (nonoptic pathway) were demonstrated in the 46 children (17%) with 1 child having two tumors. Only 1 child had symptoms referable to the tumor at the time of diagnosis. Five tumors developed in NBO that were documented on serial MR examinations. For the purpose of this article, we define NBO as areas of T2 prolongation without T1 signal change (although a small proportion have T1 shortening), no mass effect, and do not enhance after administration of gadopentetate dimeglumine (gadolinium-DTPA). Our interest in this area stems from anecdotal cases from outside our institutions where there has been apparent proliferative change in NBO.

Conclusions. NBO occur commonly in children with NF1 and are most prevalent between the ages of 4 and 10. We have shown a high frequency of brain tumors in our children with NF1, but the majority of these were asymptomatic. We have demonstrated proliferative change NBO in 11% of 46 children. Most NBO regress with age and seem to be benign, however, children with a large number and volume of NBO should be followed closely with regular MR examinations because of an increased risk of proliferative change. Pediatrics 1999; 104(4). URL: http://www.pediatrics.org/cgi/content/full/104/4/e49; neurofibromatosis type 1, magnetic resonance, tumor, astrocytoma, childhood.

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Received for publication Aug 10, 1998; accepted Apr 23, 1999.

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Neurofibromatosis type 1 (NF1) has a prevalence of ~1 in 3000 to 4000 and frequently has cutaneous and optic manifestations. The diagnosis of NF1 is most commonly made on clinical grounds in childhood and neuroimaging plays a prominent role in evaluating the extent of disease, looking for associated pathology, and for follow-up investigations. Magnetic resonance (MR) imaging is widely accepted as the imaging method of choice in children with neurofibromatosis based on its high sensitivity and specificity and lack of ionizing radiation. From the early years of MR scanning, abnormalities were demonstrated within the brains of children with NF1 that consisted of focal, well-defined areas of high signal change on T2-weighted sequences.¹⁻³ These abnormalities had not been described in the pathologic literature and were often referred to as “neurofibromatosis type 1 bright objects” (NBO). Subsequent studies demonstrated that these were common in children, but uncommon in adults, with NF1.

In this study, we investigated the prevalence of NBO in children with NF1 of different ages and followed the progression of these abnormalities on serial MR examinations. For the purpose of this article, we define NBO as areas of T2 prolongation without T1 signal change (although a small proportion have T1 shortening), no mass effect, and do not enhance after administration of gadopentetate dimeglumine (gadolinium-DTPA). Our interest in this area stems from anecdotal cases from outside our institutions where there has been apparent proliferative change in NBO.

METHODS

The MR departmental records were reviewed at the Hospital for Sick Children, Toronto, looking for clinically confirmed cases of children with NF1 who had had a brain MR examination during a 12-month period in 1992 to 1993. All cases were aged 16 years or less at the time of this examination and had the diagnosis of NF1 made by standard clinical criteria. Case histories were reviewed for clinical history for confirmation of the diagnosis of NF1, and for locating any previous or subsequent MR examinations. Therefore, there were cross-sectional and longitudinal elements to this study. Typical sequences for the brain were axial and coronal dual echo, and axial and sagittal T1W imaging. Gadolinium-DTPA was used routinely in these except in 6 children who had MR in the late
1980s, when gadolinium-DTPA was not licensed for pediatric use at our institution.

All MR examinations were reviewed by two experienced pediatric neuroradiologists (S.B., P.D.G.) and attention was paid to the number, distribution, and change of NBO and the presence of optic pathway gliomas, brain gliomas, and other intracranial pathology. Volume estimates of each NBO were made by one observer (P.D.G.). This was performed by measuring the three natural orthogonal plane dimensions of each NBO. Volume estimates were calculated using the formula:

$$\frac{4\pi}{3} \times \frac{(a+b+c)^3}{6}$$

where $a$, $b$, and $c$ are the linear dimensions in the orthogonal planes.

The NBO numbers and volumes were compared with age, sex, and the presence or absence of optic glioma.

Student’s $t$ test was used to derive $P$ values and 95% confidence intervals were calculated using standard statistical techniques. In cases in which serial examinations were available, the change in number and volume of NBO was analyzed.

Patient Summaries in Cases of MR Documentation of Tumor Development

i) In NBO

Case 1

A boy with no family history of NF1 presented at 3 years of age with a large periauricular plexiform neurofibroma and multiple cafe-au-lait lesions. He did not have macrocephaly. Initial MR at 7.5 years showed seven NBO including bilateral 0.8 x 0.8 x 0.8 cm in the globus pallidi and a small NBO (<0.5 cm) in the periaqueductal gray (Fig 1A and 1B). The NBO in the periaqueductal gray is subtle but was defined as abnormal by both neuroradiologists independently. None of the NBO had TI signal abnormalities. There was no change 3 years later, when gadolinium-DTPA was used and no enhancement was shown. Optic glioma were not present. He developed headaches at the age of 12 and an emergent computed tomography (CT) showed hydrocephalus attributable to a midbrain mass and a further mass lesion in the right globus pallidus. MR (Fig 1C–1E) confirmed the presence of two enhancing tumors at these sites (2.5 x 2.5 x 1.5 cm globus pallidus, 2.0 x 1.5 x 1.0 cm tectal tumor). Three NBO had resolved at this time.

Fig 1. Change in two neurofibromatosis type 1 bright objects in keeping with malignant proliferation (case history 1). At the age of 7.5 years, axial spin echo long repetition time (2500/90/1) images (1A and 1B) show bilateral neurofibromatosis type 1 bright objects in the globus pallidi and mild prominence of the periaqueductal gray. Note the large, plexiform neurofibroma on the left side of the scalp. At the age of 12 (Figs 1C–1E) there were two mass lesions, one in the right globus pallidus, the other in the midbrain tectum. Both abnormalities were high signal on T2-weighted images (1C) and enhanced after gadopentetate dimeglumine (1D–1E). Note that this patient did not have optic glioma so the masses present were not extensions of optic glioma.
Case 2
This girl had six cafe-au-lait lesions, axillary freckling, and bilateral Lisch nodules but no macrocephaly. She had eight NBO at presentation (none with T1 signal change) and bilateral optic nerve glioma on the original MR at 7.0 years. Her father and two siblings had NF1. An enhancing tectal tumor developed in a NBO in the periaqueductal gray matter by the time of the second MR examination at 8.8 years (Fig 2). All other NBO had resolved by the age of 10 years whereas the midbrain tumor had increased in size.

Case 3
This 4-month-old girl was noted to have multiple cafe-au-lait lesions and macrocephaly (75th centile at 5 years and >98th centile at 10 years). Her father had NF1. A preauricular plexiform neurofibroma was noted at 9 years. She had a total of six NBO on

Fig 2. Growth of a midbrain neurofibromatosis type 1 bright objects (NBO) in keeping with malignant proliferation with regression of other NBO (case history 2). At the age of 7.0 years, spin echo T2-weighted (2500/90/1) images showed bilateral NBO in the globus pallidi and mesial temporal lobes (Figs 2A–2B). There was distinct, asymmetric prominence of the periaqueductal gray matter indicating a further NBO (Fig 2A). At the age of 8.8 years (Figs 2C–2F), the repeat magnetic resonance showed hydrocephalus with regression of both NBO in the pallidi (Fig 2C). There was a mass lesion in the midbrain tectum that was high signal on T2-weighted (2500/90/1) images (Fig 2D) and low signal on T1-weighted (544/14/2) images (Fig 2E). There was marked enhancement in the mass (Fig 2F).
her first MR examination at 6.5 years and all these returned low signal on T1W images. Gadolinium-DTPA was not given on the first examination. She had glioma of both optic nerves. The NBO (Fig 3) in the left substantia nigra increased in size and showed a small enhancing focus by the time of her second examination at 7.5 years. The mass was not biopsied but continued to enlarge throughout the next 3 years (3 × 2.5 × 2.5 cm at age 10) and show greater enhancement. The other NBO remained stable.

Case 4

A boy with no family history of NF1 presented at 4 years with right proptosis and macrocephaly. Axillary and inguinal freckling was found. His original MR at 4.5 years showed bilateral optic glioma and a very heavy NBO load with 11 anatomic areas involved with 5 discrete NBO in the pons. Follow-up at 9.3 years showed a confluent infiltrating mass 4.8 × 4.0 × 3.8 cm centered in the pons but extending into the midbrain and medulla. Moderate, diffuse enhancement was demonstrated.

ii) In Apparently Normal Brain

Case 5

An 18-month-old male was found to have cutaneous neurofibroma, cafe-au-lait lesions, axillary and inguinal freckling, bilateral Lisch nodules, and macrocephaly. His father had NF1. A pre- and postcontrast brain CT and MR examinations at 6 years of age were normal and optic glioma were not present. The MR examination obtained at 8.8 years showed eight NBO and a 4.5 × 4.0 × 3.5-cm enhancing mass in the splenium of the corpus callosum. This increased in size throughout the next 2 years and biopsy showed a grade II astrocytoma.

RESULTS

The Hospital for Sick Children, Toronto, is a quan-

tinary care hospital that, during the period of this study, had 25 to 35 new cases of NF1 referred each year. Because of the referral pattern the population of NF1 cases is probably biased to children with more severe manifestations of the disease, however, it was the policy at that time to image all children with NF1 by MR at presentation whether they had central nervous system symptoms or not. Children with optic glioma or brain glioma were followed-up every 12 months by MR and children received CT and/or MR at the time of new neurologic symptoms.

During a 12-month period in 1992 to 1993, 46 children with clinically confirmed NF1 had MR imaging. There were 28 boys and 18 girls with a median age of 7.8 years and an interquartile range of 5.6 to 10.1 years. There was no statistically significant difference in age between boys and girls.

![Fig 3](https://example.com/fig3.jpg)

Fig 3. Increase in size of cerebral peduncle neurofibromatosis type 1 bright objects (NBO) in keeping with malignant proliferation (case history 3). Serial coronal T2-weighted (2500/90/1) images in the coronal plane show the evolution of the abnormality. At 6.5 years NBO are shown within the cerebral peduncles bilaterally (Fig 3A). Repeat examination at 7.5 years (Fig 3B) showed an increase in size of the left NBO that now had an enhancing central portion (not shown). The left NBO had increased in size further by 10.0 years (Fig 3C) and now had marked mass effect and showed prominent generalized enhancement (Fig 3D).
NBO at the Index MR Examination

In the original cross-sectional study NBO were found in 43 out of 46 children with NF1 with a total of 205 NBO (mean, 4.8). There were no differences between the number, volume, or distribution of NBO and sex. The anatomic distribution of NBO is shown in Table 1. The three commonest sites were: globus pallidus, 30.4%; cerebellum, 23.5%; and midbrain, 16.2%. Within the midbrain the substantia nigra was the commonest location. The number of NBO in five different age groups is shown in Figure 4. There were more NBO in children aged 4.0 to 9.9 years when compared with younger or older children. Similar trends were found with total NBO volume but with wider variation. For further statistical analysis, the children aged between 1 to 3.9 years were excluded because we assumed their full NBO complement was still evolving, producing a bivariate distribution. Comparison between age groups 4.0 to 9.9 years and 10 to 15.9 years showed statistically fewer NBO number in the older age group (younger group mean, 5.9 ± 2.5; older group mean, 2.3 ± 2.0; difference in means 3.6; 95% confidence interval, 3.0 to 4.2; t statistic, P < .01). Similar results were found with NBO total volumes (younger group mean, 4754 mm³ ± 5522, older group mean, 1338 mm³ ± 2221; difference in means 3416 mm³; 95% confidence interval, 66 to 6767 mm³; t statistic, 0.01 < P < .05). Six out of 46 (13%) patients had high signal lesions on nonenhanced T1W sequences, all these were in the globus pallidus, although 1 child had high TIW signal abnormalities lesions in the globus pallidus and substantia nigra.

Other Neuroradiologic Features on the First MR

Fifteen of 46 (33%) patients had an associated glioma involving part of the optic pathway (5 unilateral nerve; 1 bilateral nerve; 2 chiasm only; 1 unilateral nerve and chiasm; 4 bilateral nerve and chiasm; and 2 bilateral nerve, chiasm, and tracts). No difference was shown in NBO number (or volume) between the children with optic glioma and those without optic glioma (optic glioma mean, 5.8 ± 3.3; no optic glioma mean, 4.5 ± 2.7; difference in means, 1.3; 95% confidence interval, −1.7 to 4.2; t statistic, P > .10). Three children with brain tumors had optic glioma as well. Other abnormalities found were: 2 arachnoid cysts (cerebellopontine angle and anterior temporal), 1 cavernous carotid aneurysm, 2 cases of unilateral carotid occlusion producing a “moya-moya” appearance, and 2 cases of phthisis bulbi presumably as a result of a previous retinal detachment. In 1 case, MR showed a 0.5-cm enhancing mass in the left globe that was thought to be a juvenile astrocytic hamartoma. MR was repeated after a sudden decrease in acuity and left retinal detachment was shown.

Serial MR Examinations

Thirty-one children had serial MR examinations (ranging from 2 to 6) with a total of 105 follow-up examinations. The median radiologic follow-up time was 2.8 years. The serial scans showed that most children accumulate NBO when the interval scan was performed before the age of 7, with 25% gaining 5 to 8 NBO. After that age there was a tendency to stabilization of numbers in the age range 7.0 to 9.9 although 25% of children had lost 1 to 5 NBO. The tendency for NBO to regress or stabilize was maintained in the older age groups (see Fig 5).

Intrinsic Brain Tumors (ie, Excluding Optic Pathway)

Eight brain tumors were shown in 46 cases (17%), 1 child having two. The evolution of six tumors was documented by MR. Five tumors developed in previously recognized NBO. These were sited in the midbrain (n = 3), globus pallidus (n = 1), and pons (n = 1). All these abnormalities showed mass effect, increase in size, and enhancement after gadolinium-DTPA (Figs 1–3). In 1 child the documented evolution was not in a site of previous NBO (splenium of corpus callosum). All the children with tumors had a higher than average number of NBO for their age

<table>
<thead>
<tr>
<th>Anatomical Site</th>
<th>%</th>
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<tbody>
<tr>
<td>Globus pallidus</td>
<td>30.4</td>
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<tr>
<td>Cerebellum</td>
<td>23.5</td>
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<tr>
<td>Midbrain</td>
<td>16.2</td>
</tr>
<tr>
<td>Thalamus</td>
<td>10.8</td>
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<tr>
<td>Hippocampus and amygdala</td>
<td>10.3</td>
</tr>
<tr>
<td>Pons</td>
<td>4.4</td>
</tr>
<tr>
<td>Medulla</td>
<td>3.4</td>
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<tr>
<td>Internal capsule</td>
<td>0.5</td>
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<td>Putamen</td>
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group, although this did not reach a statistical significance level of 5%. Only 1 child had symptoms referable to the tumor at the time of diagnosis (case 4).

**DISCUSSION**

NF1 is an autosomal dominant condition with a penetrance of nearly 100% and an estimated spontaneous mutation rate of 50%, with the single gene abnormality localized on chromosome 17.\(^5\) Intracranial manifestations of NF1 are among the most frequent and are often the most disabling. The diagnosis of NF1 is usually made in childhood by clinical examination and there is a positive family history in 50% of cases. Neuroimaging can be used to evaluate the extent of the disease, look for associated abnormalities, and follow the progression of complications. The commonest malignant central nervous system complication is optic/hypothalamic glioma that occurs in 5% to 15% of NF1 cases\(^6,7\) and is the usual reason for follow-up imaging. Brain (nonoptic) glioma are thought to occur in up to 3.5% of cases\(^8\) and also require follow-up imaging. Gliomas in NF1 tend to present earlier and are more likely to be multifocal than those not occurring in NF1.\(^9\) Cerebellar tumors are known to have a poor prognosis,\(^10\) whereas brainstem tumors seem to be a distinct clinical entity with a favorable prognosis.\(^11\) Tumor stabilization and regression without treatment are recognized. Other established cranial/intracranial manifestations include sphenoid dysplasia, aqueductal stenosis, neurofibromas, occlusive vascular disease, aneurysms, and hemimegalencephaly. MR is preferred to CT in the initial examination and follow-up of children with NF1 on the grounds of higher sensitivity for most associated pathologies and because of the lack of ionizing radiation.\(^3,15,16\)

Abnormal high signal areas on T2-weighted MR images (NBO) were recognized in the early days of MR. These abnormalities were not described in the pathology literature and were not found on earlier CT examinations (although subsequently have been shown in the globus pallidus).

MR studies describe an overall NBO frequency of 43% to 77% in NF1\(^3,15\) and were considered pathognomonic of NF1 by some authors. NBO were found most commonly in the basal ganglia, brainstem, cerebellum, and occasionally in the subcortical white matter and dentate nuclei\(^15,16,19,20\) The globus pallidus was often reported as the commonest site, usually with bilateral involvement,\(^15,21\) and this is supported by our findings. However, Sevick et al\(^22\) found 49% of NBO in the cerebellum (peduncles and hemispheric white matter, 22% in the medulla and pons, 10% in the midbrain, and 19% in the supratentorial white matter) in their study of 43 patients. Aoki et al\(^3\) also report the cerebellum was the commonest site, followed by the pons, globus pallidus, and midbrain. NBO are typically isointense with white matter on T1-weighted scans, do not have surrounding edema or mass effect, and do not enhance with gadolinium. They do not seem to be responsible for any neurologic deficits.\(^3,15,17,18,22\) Other MR studies have raised the possibility of two distinct types of lesions. Basal ganglia NBO sometimes show T1 prolongation, some mass effect, and it has been postulated that these may be Schwann cell or melanocyte-containing hamartomas.\(^15,22\)

NBO are reported most frequently in children and are rare in patients older than the age of 20 years. Itoh et al\(^19\) reported NBO in 93% of their patients younger than 15 years of age, 57% of those aged 16 to 30 years, and 29% of those older than 30. The frequency quoted in that article for children is identical with that reported in the present study. Itoh et al\(^19\) found that although lesions in the basal ganglia, internal capsule, and brainstem were seen in all age groups, cerebellar and dentate nucleus lesions were rare after the third decade and were seen mainly in children younger than 10 years of age.

Cerebellar NBO were shown to decrease in size with age although some may remain static or even increase in size.\(^17,19,22\) Any increase in size in patients older than 10 years of age warrants close follow-up to rule out neoplasm.\(^22\)

Some of the lesions had mass effect and others occurred in conjunction with gliomas raising the possibility of their having malignant potential.\(^19\) In this article we have shown age-related change in NBO that does not seem to show significant variation from one anatomic site to the next.

Most authors describe NBO as benign lesions such as hamartomas, heterotopia, or dysplasias.\(^1,17,23,24\) It is clear that the behavior and signal characteristics of
NBO do not fit with the pathologies listed above. Further hypotheses are zones of gliosis or low grade tumors and it has been suggested that they could be areas of dysmyelination where abnormal myelin has been broken down as the patients mature. There have been few opportunities for histopathologic analysis of NBO.

A stereotactic biopsy of a white matter lesion showed normal brain tissue (E. K. Schorry; presented at the Annual Clinical Care Conference at the National Neurofibromatosis Foundation, Oct 1988). Di Paolo et al reported postmortem studies on two 10-year-old girls with T2-weighted MR abnormalities in the internal capsule and globus pallidus who died from complications of neurofibromatosis and a neonate with diffuse infra- and supratentorial hyperintense white matter. They found intramyelinic vacuoles 5 to 100 μm in diameter with no stainable material in them on all three patients. They postulated that transient spongiori intramyelinic change accounted for the characteristic T2-weighted lesions and explained their age-related changes.

One of their patients showed diffuse proliferation of protoplasmic astroglia particularly in the globus pallidus, substantia nigra, and dentate nucleus. The glia of the globus pallidus contained unusual, crinkled, or twisted nuclei and the changes in this patient were thought to be reactive. Two of Ferner et al’s adult patients underwent postmortem examinations and were found to have areas of ischemia corresponding to the previously noted T2-weighted MR hyperintensities in the periventricular areas, pons, and cerebellum. Significantly, there was no evidence of heterotopia or hamartomas in either patient. The nature and significance of NBO remain unclear and there are several important questions concerning the nature of NBO. These include: What do NBO represent? What happens to them in childhood? How should children with NBO be investigated? Our findings provide some insight to these problems. Children younger than the age of 4 have few NBO but these develop rapidly to produce maximal numbers and volumes between 4 and 10 years. This is followed by a reduction in maximal number and volume that continues from late childhood to early adulthood. Brain tumors were found in a significant number of children with NF1 (15% in the current report—much higher than usually quoted and with a 5:2 male to female ratio) and the majority of these did not cause significant neurologic symptoms. Five tumors were shown to develop in regions previously diagnosed as NBO. All children with brain tumors had a higher number of NBO than average when compared with children in their age groups.

These findings suggest that not all NBO are benign and a case could be made for regular follow-up of children with NF1, particularly of children with a large number of NBO between the ages of 7 to 12 years. However, an alternative explanation is that the lesions that were called NBO by neuroradiologists originally were in fact early gliomas and that malignant change did not occur in an NBO per se. Our data cannot distinguish between these two hypothesized but two important points arise from this discussion. It is vital that these patients are investigated by MR, not CT, and that gadolinium-DTPA is given on the first examination in all cases of NFI referred for brain MR and on follow-up examinations if there has been any change. At present, gadolinium-DTPA enhancement is the best indication of malignancy although techniques such as spectroscopy remain to be tested. Secondly, if there is any suggestion of atypical findings, follow-up examinations should be performed.

CONCLUSION

In summary, we have shown that NBO are exceptionally common in children with NF1 and that NBO evolve during the early years of childhood. Most NBO follow a benign course and will reduce in size and ultimately disappear, however in 5 out of 46 of our cases NBO changed, increasing in size and enhancing as a would a malignant tumor. Our results raise some concern about the benign history of all NBO but our work should be taken as preliminary as only one of the masses was biopsied. The lack of symptoms and inaccessible anatomy of the tumors produced a wait-and-watch approach and further studies are necessary to come to firm conclusions. It is important for pediatricians and radiologists to be aware of this potential complication of NFI. At present the recommendations put forward by the Committee on Genetics of the American Academy of Pediatrics do not include follow-up MR examination of asymptomatic children with NFI, although optic gliomas should be followed-up. However, our work indicates that it may be necessary to follow-up some children with NF1 if they have a large number of NBO or atypical NBO particularly between the ages of 7 and 12 years.

ACKNOWLEDGMENTS

This work has been supported in part by the Academic Links Scheme of the British Council of Canada.

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