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Central nervous system imaging in reevaluation of patients with neurofibromatosis type 1

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Abstract. We report the results of the reevaluation of 24 patients with neurofibromatosis type 1 (NF1) using central nervous system (CNS) imaging techniques. The first examination by computed tomography (CT) or magnetic resonance imaging (MRI) indicated the presence of optic glioma in three cases, "unidentified bright objects" (UBOs) in six, and a suspected right frontal tumor in one. In two patients optic glioma and UBOs were both present and in one of them a bulbar tumor was also suspected. Later imaging examinations revealed the appearance of optic glioma in three more cases and UBOs in nine. In two of these patients both optic glioma and UBOs were present. This study indicates that the likelihood of detecting imaging abnormalities in patients with NF1 increases when systematic follow-up is performed. Optic gliomas are characteristic of pediatric patients; they rarely give rise to clinical manifestations (1/6 cases) and in general progress very slowly. For these reasons, therapeutic strategy must be carefully considered and individually decided. UBOs are very frequent findings in pediatric patients with NF 1 and therefore they must be considered diagnostically relevant. They are not related to clinical manifestations and spontaneous regression has been observed. The nature of these imaging abnormalities is still unknown, but because they do not behave like tumors, useless and dangerous therapeutic procedures should not be employed.

Key words: Neurofibromatosis type 1 – Magnetic resonance imaging – Computed tomography – Central nervous system imaging abnormalities

Introduction

Central nervous system (CNS) tumors, in particular optic pathway gliomas (OGs), are well-known findings associated with neurofibromatosis type 1 (NF1). Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain have greatly increased our knowledge of the incidence and natural history of these tumors. The more widespread use of these neuroimaging techniques, especially MRI, has allowed detection of the presence of cerebral areas that appear hypodense on CT and have an increased signal on T2-weighted MR images. These abnormalities have been noted since 1986 by Cohen et al. [4] and are frequently found in the basal ganglia, internal capsule, brain stem, and cerebellum. The images are characterized by the absence of mass effect or surrounding edema, and apparently are not associated with developmental disabilities [7]. Since their precise nature is still unknown, these findings have been dubbed "unidentified bright objects" (UBOs).

Our protocol of investigations in patients with a diagnosis of NF1 includes periodic CT scans or MRI of the brain in order to identify the presence of CNS tumors or optic gliomas. This systematic imaging program, in addition to early detection and follow-up of optic gliomas, has also given us the chance to document the behavior of the UBOs and learn more about their nature. In this paper we report the results of this neuroimaging follow-up study of 24 subjects with NF1.

Patients and methods

In 38 patients with a diagnosis of NF1 established on the basis of the criteria of the Consensus Development Statement of the National Institutes of Health [13], brain CT scanning was performed as the first examination in 27 cases and MRI in 11. The average age of the subjects was 7 years 8 months (range 6 months to 27 years 6 months).

CT findings were normal in 14 cases. An optic glioma was demonstrated in 1 case and UBOs in 2. In 1 patient an area of hypodensity in the right frontal region was suggestive of a cerebral tumor. Findings apparently unrelated to NF1 were observed in 9 cases (cerebral ventricular enlargement, septum pellucidum cyst, cerebral hemiatrophy). MRI findings were normal in 6 cases. UBOs were present in 3 patients and optic glioma plus UBOs in 2, associated in 1 case with a bulbar hyperintense area. Because of the presence of episodic dizziness, pallor, vomiting, and a mild mass effect, this area was considered to be suspect for a bulbar tumor.

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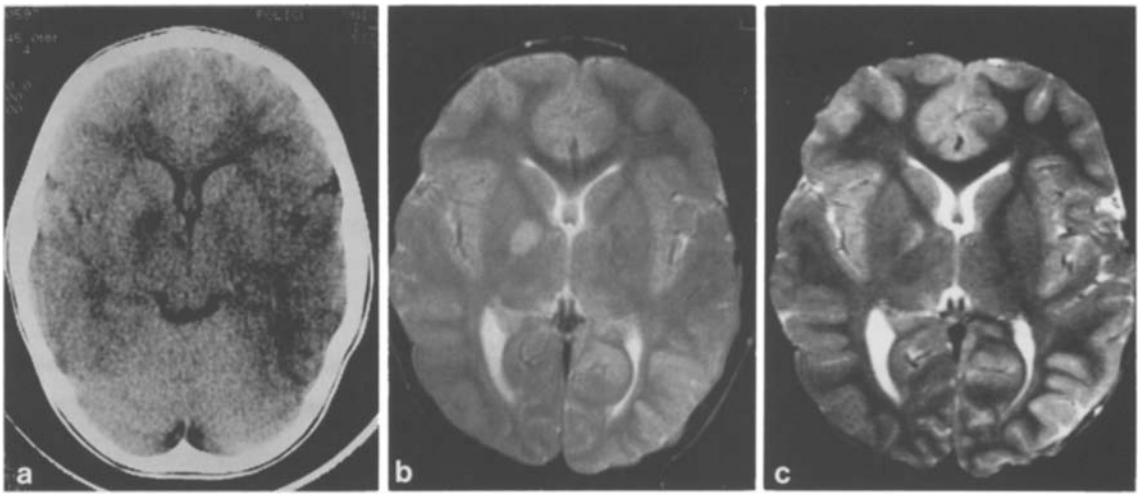

Fig. 1. a Brain computed tomographic (CT) scan at the age of 5 years 2 months: an area of hypodensity is present in the right globus pallidus and internal capsule. **b** Brain magnetic resonance image (MRI) at the age of 8 years: an area of increased signal is present in the right globus pallidus and internal capsule on T2-weighted images. **c** Brain MRI at the age of 9 years 6 months: the area of increased signal on T2-weighted images is markedly reduced in size

Table 1. Results of follow-up imaging in patients with abnormalities at first examination. I, II, III, IV: Sequential examinations performed in the same patient. CT, Computed tomography; MRI, magnetic resonance imaging; OG, optic glioma; UBO, single "unidentified bright object"; UBOs, multiple "unidentified bright objects"; FT, frontal tumor; BT, bulbar tumor

Patient	CT	CT	CT	MRI	MRI	MRI
1	I UBO			II UBOs		
2	I UBO			II UBO	III UBO	IV UBOs
3	I FT?			II FT	III FT	
4	I OG	II OG	III OG			
5				I UBOs	II UBOs	
6				I UBOs	II UBOs+OG	
7				I OG+UBOs+BT?	II OG+UBOs+BT?	
8				I OG+UBOs	II OG+UBOs	III OG+UBOs

In the patients whose first imaging examination indicated abnormalities, we tried to obtain yearly examinations subsequently. It was possible to perform 3 further examinations in 1 case, 2 in 3 cases, and 1 in 4 cases. In the subjects whose first examination was normal or showed aspecific findings, subsequent examinations were scheduled every 3 years. We were able to obtain 4 subsequent examinations in 1 case, 3 in 5 cases, 2 in 6 cases, and 1 in 4 cases. Whenever possible, MRI was always preferred to CT scan for the follow-up.

Results

Patients with imaging abnormalities at first examination

Among the patients in this group, the first examination was performed by CT scan in four cases (patients 1–4) and by MRI in the other four (patients 5–8; Table 1). This examination demonstrated the presence of a single UBO in patients 1 and 2 and multiple UBOs in patients 5 and 6. These abnormalities were observed in patients whose ages ranged from 5 years 2 months to 11 years 8 months. The follow-up imaging of these four patients indicated the appearance of multiple UBOs in patient 1, no change in patient 5, and the presence of an optic glioma in patient 6 at the age of 11 years 2 months. In patient 2, who showed a single UBO localized to the right globus pallidus and internal capsule, a marked reduction in size of the UBO was noted at the age of 9 years 3 months (Fig. 1). At this time, a further hyperintense area was evident in the left globus pallidus.

Among the other four cases, patient 3 had an imaging abnormality observed at the age of 2 years 6 months suggestive of a frontal tumor. On the following MRI, this area appeared hyperintense with a central hypointense signal, indicating a cystic tumor (hamartomas?). In patient 4, a left optic glioma extending to the optic and suprasellar regions was demonstrated at the age of 11 years 10 months. Because the patient's visual acuity was reduced, a surgical intervention limited to the optic nerve was performed in another hospital. No modification in the residual tumor size was observed on the following two CT scans. In the last two patients (nos. 7 and 8) UBOs and optic glioma, associated in patient 7 with a possible bulbar tumor, were observed at the ages of 5 years 4 months and 3 years 3 months, respectively. These findings remained unchanged at the subsequent examinations.

Table 2. Results of follow-up imaging in patients with normal or aspecific findings at first examination. N, Normal; A, aspecific findings

Patient	CT	CT	MRI	MRI	MRI
1	I N	II OG+ UBOs	III OG+ UBOs	IV OG+ UBOs	V OG+ UBOs
2	I A	II A	III A	IV A+UBOs	
3	I A	II A	III A		
4	I A	II A	III A	IV A	
5	I A	II A	III A	IV A	
6	I A		II A+ UBOs	III A+ UBOs	III A+ UBOs
7	I A		II A+ UBOs		
8	I A		II A+ UBOs		
9	I N		II UBOs	III UBOs	IV UBOs
10	I N		II UBO	III UBOs	
11	I A		II A+ UBOs	III A+UBOs	
12	I N		II UBOs	III UBOs	
13	I N		II OG	III OG	IV OG
14	I N		II N		
15	I N		II N	III N	
16	I N		II N		

Patients with normal images or aspecific findings at first examination

In all 16 patients belonging to this group the first examination was performed with CT scan (Table 2). In 5 of these cases (patients 1–5) a second CT scan was carried out before one or more MRI and in the other 11 cases (patients 6–16) MRI was always used for the follow-up.

The follow-up imaging indicated the presence of UBOs and optic glioma at the age of 4 years 4 months in patient 1. In 8 patients (nos. 2, 6, 7–12), UBOs were observed at ages ranging from 4 years 6 months to 19 years 6 months. UBOs were multiple in all cases but one (patient 10). In patient 13, optic glioma was noted at the age of 10 years 10 months. In the remaining 6 cases (patients 3–5, 14–16) no abnormalities were discovered.

Further MRI in patients with UBOs and/or optic glioma did not indicate any change in these images, except in patient 10, in whom multiple UBOs were later demonstrated.

Summary of results

Of 24 patients in whom two or more brain images were obtained, imaging abnormalities related to NF1 were observed in 18. Optic gliomas were present in 6 cases, UBOs in 15 cases, and brain tumors in 2.

The mean age at which optic gliomas were observed was 7 years 9 months. These tumors were asymptomatic in 5/6 cases.

The mean age at which UBOs were observed for the first time was 8 years 6 months. These entities, which became multiple in all patients, were localized to basal nuclei (12 cases), internal capsule (9 cases), cerebellum (11 cases), brain stem (12 cases), thalamus (2 cases), and subcortical white matter (11 cases). They did not cause any symptoms in any case.

UBOs and optic gliomas appeared together in the same patient in 4 cases.

Discussion

Our study shows that three out of four patients with NF1 present with imaging abnormalities correlated with the disease.

Optic gliomas are the most frequent tumors observed in NF1. Their incidence is reported to range between 4% and 36% [2, 3, 8, 10, 14]. This wide range is probably due to the age at which imaging examinations are performed [8], or to the fact that these tumors are frequently asymptomatic and therefore the patients are not systematically investigated by neuroimaging [2].

In our series, the presence of optic gliomas was observed in 6 cases out of 24. In 3 patients, these tumors were present at the first examination. In the other 3, they were observed on subsequent evaluations. It is therefore evident that the chances of detecting the presence of optic gliomas increase when a systematic follow-up is performed.

The mean age of patients with optic glioma is reported to range between 4.5 and 9.8 years [2, 10, 11]. In our cases, the mean age at which optic gliomas were documented for the first time was 7 years 9 months (range 3 years 3 months to 11 years 10 months). These data indicate that these tumors are peculiar to the pediatric age group.

Optic gliomas are reported to have a very slow progression in some cases [1, 6, 10]. Moreover, they give rise to clinical manifestations in only 20%–30% of patients [10, 15]. The average period of follow-up in our cases was 2 years 7 months (range 9 months to 5 years 9 months), and progression of these tumors or related symptoms was not observed in any case but one. Because of these peculiar characteristics, we agree with the opinion that surgical, radio- or chemotherapy is indicated only in rapidly progressing tumors that are causing clinical symptoms [15, 19]. Therefore these tumors can be monitored only by clinical and campimetric assessment. Periodic neuroimaging examination might be indicated in younger, uncooperative patients. Recently, visual evoked potentials have been reported to be a sensitive test for the presence of optic glioma [11].

The presence of the strange brain images denominated by the acronym "UBO" has been reported in 60%–70% of patients with NF1 [2, 5, 18]. Similar findings have occasionally been detected in adults, but they have rarely been observed in children and adolescents without NF1 [16].

In our series, UBOs were present in 15 patients out 24. In 6 of these the UBOs were already evident at the first examination and the periodic imaging follow-up revealed the presence of UBOs in 9 more cases. The results of our study do not allow a precise definition of the age at which these abnormalities first appeared, but the mean age at

which they were noted for the first time was 8 years 6 months. Thus, UBOs appear to be typical of the pediatric age group.

The follow-up indicates that further similar images can appear in the same patient. However, a tendency to progress has been never documented over a mean observation period of 3 years (range 9 months to 9 years).

The origin and the nature of UBOs is still unknown. The possibility of a gliomatous, hamartomatous, heterotopic, or dysplastic origin has been considered [3, 5, 7, 9, 16]. Since cerebral ischemia is not infrequent in NF1, UBOs have also been considered as areas of defective blood supply due to dysplasia of cerebral vessels [8]. Increased free water content has also been suggested [8]. The possibility of heterotopic areas containing Schwann cells or melanin deposits has been considered on the basis of a hyperintense signal observed on T1-weighted images in some patients [12].

Histopathologic examination of the involved cerebral tissue, performed in one case, found no abnormalities [17].

In one of our patients, a marked reduction in size of the hyperintense area was documented over a period of 1 year 6 months. Duffner et al. [5] reported a similar phenomenon in a 2-year-old-boy. These data, along with the lack of any clinical manifestations related to the presence of these imaging abnormalities, speak against the likelihood that UBOs are neoplastic in nature.

Aoki et al. [2] reported that UBOs are more frequent in presence of optic gliomas. However, in our series, of 16 patients with UBOs, optic gliomas were found in 4, i.e., the same incidence as in all our NF1 patients (6/24). Therefore, considering the high incidence of both UBOs and optic gliomas in NF1, the association of these entities in the same patients may be only casual.

Conclusions

Optic gliomas are frequently found in pediatric patients with NF1. Therefore, a schedule of systematic imaging examinations is indicated once the diagnosis of NF1 has been established. However, the therapeutic strategy in patients in whom these tumors are found must be decided individually, and invasive treatment should be considered only in the presence of rapidly progressive and symptomatic lesions.

UBOs are very frequent findings in NF1. Because of their high incidence in younger patients, they must be considered of diagnostic relevance in this age group. Although their nature is still unknown, these imaging abnormalities should not be regarded as tumors, and no useless or dangerous therapeutic procedures should be undertaken in relation to them.

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