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Cerebellar gliomas in children with NF1: pathology and surgery

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Abstract Cerebellar gliomas associated with NF1 (CGNF1) are rarely reported in the literature, and they are considered to be malignant in a high proportion of cases. In an attempt to improve the definition of this disease and clarify its management, we reviewed our patients with CGNF1 and compared their tumors with sporadic cerebellar gliomas (SGC). We operated on six children with CGNF1, all but one of whom were asymptomatic. They represented one-tenth of all pediatric cerebellar gliomas, and one third of NF1-associated gliomas seen in our institution. CGNF1 appeared at a later age than SCG. They are seated near the roof of the IV ventricle and are not related to white matter hypersignal hamartomas. Most of these tumors showed radiological progression. They were four pilocytic astrocytomas, one ganglioglioma, and one malignant astrocytoma. One patient had tumor recurrence after 8 years, and the others are still disease free. The overall outcome appeared to be better for GCNF1 than for SCG. On account of the regular growth, uncertain pathology, and good surgical outcome, we advocate systematic resection of these tumors.

Keywords Neurofibromatosis type 1 · Cerebellar neoplasms · Pilocytic astrocytoma · Anaplastic astrocytoma · Ganglioglioma · Tumor growth rate

Introduction

Although neurofibromatosis type I (NF1) was initially described as "peripheral" neurofibromatosis, it is associated with tumors of the central nervous system in as many as 5% of cases [8]. These tumors are mainly gliomas, mostly involving the optic tract and the hypothalamus. Although less common, cerebellar gliomas are not exceptional, and occupy the second place in terms of frequency in the study of NF1-associated gliomas published by Ilgren et al. [4]. The prognosis of cerebellar gliomas associated with NF1 (CGNF1) is not well established, but many authors consider that they are more malignant than sporadic cerebellar gliomas (SCG) [2, 7, 9]. However, the rare series reported in the literature are old and small [4, 11], and both the pathology and the natural history of CGNF1 are still poorly understood [15]. The diagnosis of these tumors has benefited greatly from the advent of computerized radiology, and most tumors are now diagnosed at an asymptomatic stage by systematic MRI. At the same time, it is often not clearly evident when surgical treatment for these benign lesions is warrented on account of the technical problem of intraoperative guidance for the removal of these deep, small tumors.

We reviewed the cases of pediatric CGNF1 operated on in our department and compared these with SCG, with particular attention to spontaneous behavior, pathology, and outcome after surgery.

Case reports

From 1986 to 1999, a diagnosis of cerebellar glioma was made in six children with NF1 in our department. All these patients were

Table 1 Cerebellar gliomas in NF1

Patient	Sex	Age (years)	NF1 history	Symptoms	Tumor progression	Interval (years)	Pathology	Follow-up (months)	Outcome
1	F	10.5	Optic glioma	Asymptomatic	559%	4.1	Ganglioglioma	8	Disease free
2	M	19	Aqueductal stenosis	Ataxia, herniation	700%	4.2	Pilocytic	127	Dead[a] (disease free)
3	F	8	Scoliosis	Asymptomatic	33%	0.5	Pilocytic	4	Disease free
4	M	12.5	Spinal neuroma	Asymptomatic	0%	0.4	Pilocytic	26	Disease free
5	F	8	None	Asymptomatic			Pilocytic	88	Recurrence after 8 years
6	F	9	Optic glioma	Asymptomatic	95%	0.3	Anaplastic astrocytoma	147	Disease free

[a] Patient 2 died in an unrelated traffic accident

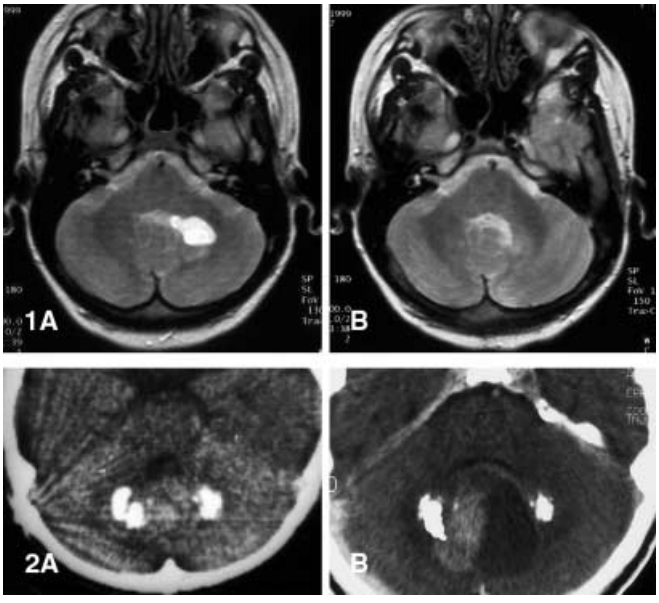

Fig. 1 A,B T2-weighted MRI scan, axial and frontal views, in case 3. **A** Preoperative image: the tumor has a typical rounded appearance, situated in the depth of the cerebellar hemisphere, with no mass effect on the IV ventricle. The pathological diagnosis was pilocytic astrocytoma. A previous MR scan 6 years previously, performed as a control for optic tract astrocytoma, disclosed no cerebellar tumor. **B** Postoperative image after removal using frameless stereotaxy. The use of image-guided surgery is crucial for the total and safe removal of such small, deep-seated lesions

Fig. 2 A,B Repeated CT scan and MRI for patient 2, taken 4 years apart. **A** The patient had aqueductal stenosis with hydrocephalus, and the cerebellar calcifications were initially interpreted as Fahr's disease because of the absence of contrast uptake and mass effect. **B** CT scan was repeated because of symptoms of raised intracranial pressure and ataxia raising the initial diagnosis of shunt failure

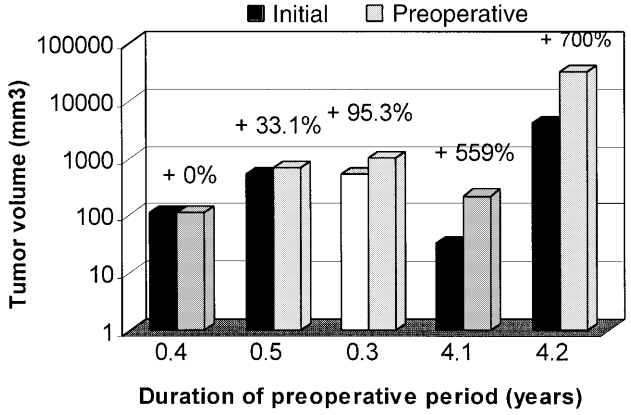

Fig. 3 Tumor volume at the time of diagnosis and at the time of surgery for five patients, represented on the *y*- axis on a logarithmic scale. *Figures* above *bars* indicate the observed growth rate during the time interval indicated below *bars*. The lesions had variable growth rates, the highest value being noted in the third case (□), which had compounded growth estimated at 750% a year, associated with an anaplastic astrocytoma

operated on, because of symptoms related to the tumor, documented growth of the lesion, or on account of hazardous behavior as reported in the literature. The clinical, radiological and pathological features are summarized in Table 1. The mean age of patients with CGFN1 was 12.2±4 years. During the same period, we treated 65 children with SCG (mean age 8.2±4.4 years) and 17 NF1 patients with optic tract glioma (mean age 6.3 years). In all GCNF1 cases, NF1 had been diagnosed several years earlier. Two patients were followed up for optic tract glioma, two had scoliosis, and one had a lumbar neuroma. One patient had hydrocephalus secondary to stenosis of the aqueduct, which had been diagnosed and shunted 11 years previously. Five of the six patients had developmental delay requiring educational intervention. In no case was a history of glioma reported in NF1-affected relatives.

At the time of diagnosis, only one CGNF1 patient had symptoms related to the tumor (ataxia and dilated pupil), which was initially misdiagnosed as shunt obstruction. In the five others, CT (one case) or MRI (four cases) was performed as a routine check-up for NF1 or as a control in the follow-up after treatment for optic tract glioma. Among 65 SCG, only 1 tumor was asymptomatic (diagnosed after minor head trauma), and 42 of the 65 patients had hydrocephalus requiring some measure of cerebrospinal fluid diversion.

Imaging of the CGNF1 showed a characteristic rounded, homogeneous, non-cystic tumor, developing in the subependymal white matter near the fastigeal and interpositus nuclei (Fig. 1). In one case, the lesion was cystic and calcified (Fig. 2). The diameter of the CGNF1 ranged from 6 to 40 mm, with mass effect in the latter case only. Two patients with CGNF1 had negative CT scan or MRI, two years and five years respectively before the diagnosis. In five cases with CGNF1, the CT or MRI was repeated between the diagnosis and surgery, allowing an estimation of the growth rate (Fig. 3). In SCG, only 42/62 cases had no cystic com-

ponent, and mass effect was present in all cases. All SCG cases were operated on quickly, allowing no estimation of the growth rate.

In two CGNF1 cases, adjunctive intraoperative ultrasonography was needed for tumor location. One patient needed early reoperation for complete removal of the tumor. The two latest cases were operated on using frameless stereotaxy (Stealth station, Sofamor-Danek).

The pathological diagnosis for CGNF1 was pilocytic astrocytoma in four cases, anaplastic astrocytoma in one case, and ganglioglioma in the sixth case. Several tumors were atypical in some respect: hypervascularity was found in three cases, mixed neuroglial features in one, and malignancy in one other. Thus, only two cases had a regular type of pilocytic astrocytoma. In contrast, SCG were generally (56/62) pilocytic astrocytomas, only 3 of the 62 having a malignant tumor.

Low-grade CGNF1 received no postoperative treatment. The patient with anaplastic astrocytoma had external irradiation (50 Gy to the posterior fossa). The postoperative follow-up ranged from 4 months to 12 years (mean 63.2 months), during which one patient died of a traffic accident 10.5 years after surgery, with no evidence of a recurrence at the latest control. Only one patient is symptomatic, with mild ataxia but living a normal life. One patient with a pilocytic astrocytoma, who was tumor-free according to the initial postoperative MRI, presented with a local recurrence 8 years later and was operated on again, with complete removal. All four others, including the patient with anaplastic astrocytoma, are tumor free on MRI scans performed 4 months to 13 years after surgery (mean 54.8 months). In the SCG group, one 12-month infant died postoperatively, 14 patients have ataxia, generally of mild intensity, and six have visual disturbances of varying degrees of severity. After a mean follow-up period of 44 months, 2 SCG patients died of tumor progression, 53 are disease-free, and 9 have stable tumor remnants on MRI (on average 27 months postoperatively).

Discussion

Tumors of the central nervous system occur in 5–11% of patients with NF1 [4]. In contrast to adults, for whom the main cause of mortality is malignant degeneration of a neurofibroma, gliomas are the main cause of mortality for children with NF1 [1]. For the neurosurgeon, cerebellar gliomas, along with optic nerve gliomas, are among the few surgically curable lesions associated with NF1. With a more fundamental approach, these lesions raise the question of their relation with a mutation in the neurofibromin gene. In a practical approach, they pose the problem of whether or not to operate, that is to say: What is their spontaneous behavior like? What are the risks of surgery? and Does the benefit justify the risk?

The true incidence of cerebellar gliomas in NF1 cannot be derived from our study, which is based on surgical experience. It can be estimated at one-tenth of pediatric cerebellar gliomas, and one-fourth of children with NF1 referred to our department. In our experience, patients with CGNF1 were older than those with NF1-associated optic gliomas, which could suggest that the glial migration and maturation patterns under the dependence of the neurofibromin are different in these two sites. In addition, two of our patients had an optic tract glioma several years before the occurrence of CGNF1, a finding reported earlier [5], which could suggest the existence of a subset of NF1 patients with greater than normal vulnerability for glial tumors. Future genetic studies could yield molecular support for these hypotheses. Our patients with CGNF1 were also older than patients with SCG, despite a much smaller tumor volume. This suggests that the growth rate is slower in CGNF1 than in SCG, in contrast with earlier findings [2, 4, 10].

The tumors in our series regularly appeared in the subependymal white matter of the IV ventricle near the interposed nuclei. This feature could be compared with the typical subependymal situation of giant-cell astrocytomas of the lateral ventricles in tuberous sclerosis. It could be related, in both phakomatoses, to a disturbance of maturation and migration of the astrocytic precursor, since neurofibromin is involved in cell migration and differentiation, in addition to oncogene suppression [15]. Carella et al. postulated that these tumors could result from the degeneration of white matter hamartomatous lesions known as unidentified bright objects (UBO) [2]. However, the region of the roof of the IV ventricle is not a common site for UBO [3, 12], and the findings in our patients, with MRI performed soon after, or even before, the appearance of the tumor, do not substantiate this view. The absence of cyst associated with the tumor in most cases of CGNF1 is probably connected with the early diagnosis of these lesions, and not a characteristic of CGNF1, since the only symptomatic CGNF1 was cystic, whereas the only asymptomatic SCG was noncystic.

The scope of glial tumors associated with NF1 is wide, and enlarges with new case reports and improving immunostaining techniques. The occurrence of gangliogliomas in NF1 is established [6], but has not yet been reported in the cerebellum. The general assumption is that these tumors have no specific characteristics and are histologically identical to sporadic tumors [14]. In our patients, however, typical pilocytic astrocytomas, which are prevalent in GCS, appeared to be outnumbered by nonpilocytic or atypical pilocytic tumors, suggesting that CGNF1 represent a different subset of gliomas.

The incidence of malignancy in CGNF1 is debatable, the data are scarce and often old, published before the WHO classification, and the criteria retained for malignancy are often not clear. Ilgren et al. reported on 15 cases of cerebellar glioma associated with neurofibromatosis, apparently of type 1, collected since 1940 [4]. Many patients were adults; 8 cases were considered malignant, and mortality was high, reflecting the poor prognosis of posterior fossa surgery in earlier times. Among ten cases reported by Bigner et al., two were histologically malignant, a proportion similar to our findings [1]. In a more recent series, the behavior of CGNF1 was not considered different from SCG, but many of these CGNF1 were fibrillary and not pilocytic [13], a finding not confirmed in other series. In our experience, tumor growth, quantified on MR scans, was uneven but gener-

ally slow, although comparative data for SCG are absent in the literature. A single case in our series showed rapid growth correlated with histological malignancy.

The management of CGNF1 is based on surgical resection, and the indications for surgery are generally broad [7]. This attitude is opposed to the commonly accepted conservative attitude to NF1-associated optic tract gliomas, which are generally treated only when there is symptomatic growth. This discrepancy rests on the differences in behavior and surgical resectability of these two lesions. CGNF1 are generally small and well separated from the surrounding tissues, and can be totally and safely resected, especially with the help of neuronavigation techniques. We had no mortality and minimal morbidity in CGNF1. In contrast, SCG are symptomatic, larger tumors, often operated on as emergency procedures in younger children or in infants, and they involve a higher morbidity or even mortality. Thus, the surgical results obtained in these two groups can be compared only if these major biases are taken into account.

In spite of a more benign behavior than reported earlier, we think that surgical removal of CGNF1 should be proposed whenever possible. We consider that the uncertainties about malignancy, and the regularly progressive nature of these lesions, are strong enough incentives in favor of surgery in these patients, to say nothing of the psychological benefit of getting rid of a brain tumor, however benign. The late recurrence in one of our cases, despite the absence of any detectable tumor remnant on postoperative MRI, indicates that the clinical and radiological follow-up of these patients must extend over a long period.

In conclusion, the pathological, clinical, and radiological features of CGNF1 set them apart from SCG. These characters could give an insight into their relation with the mutation of the *NF1* gene. The majority of these tumors are benign, and they generally have a more indolent behavior than SCG. Although it is less frequent than reported earlier, malignancy is a possibility that cannot be predicted from a single radiological study. Malignant tumors can be discerned from benign lesions only with repeated radiological imaging, or after surgical removal. Surgical treatment of these tumors is safe, especially with the help of neuronavigation for location of these small, deep lesions. In our opinion, the risks of tumor progression combined with the safety of the surgery make systematic removal advisable.

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