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Systematic MRI in NF1 children under six years of age for the diagnosis of optic pathway gliomas. Study and outcome of a French cohort

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ABSTRACT

Background/Purpose: Optic pathway glioma (OPG) is the most common central nervous system tumor in children with neurofibromatosis type 1 (NF1), affecting 15–20% of patients. We reviewed the medical records of children systematically screened by ophthalmologic and MRI examinations to determine the influence of screening on the therapeutic management of children with OPG.

Methods: Data were collected on 306 newly diagnosed cases screened with systematic MRI from January 2001 to July 2007. In the OPG group, we distinguished the asymptomatic or symptomatic groups according to their initial status.

Results: Forty-five patients had confirmed OPG (14.7%). Thirty-six patients (80%) were asymptomatic and nine (20%) were symptomatic at the time of diagnosis with visual symptoms in six cases. The average age at OPG diagnosis was 3.4 years with six patients (13%) over six years old. Average follow-up was 7.7 years. Progression was observed in 16

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cases (35%). Most patient conditions were managed conservatively (87%). Six children (13%) were treated with chemotherapy due to worsening visual function. All of these children had severe or mild visual impairment at the end of follow-up.

Conclusion: Our study does not support a clear benefit of systematic MRI screening in NF1 children under six years old. Systematic neuroimaging in our study did not influence therapeutic management. Although OPG diagnosis was made early, treatment with chemotherapy did not improve the final visual outcome. If MRI remains the best tool for the diagnosis of cerebral and spinal pathologies in the NF1 population, our current study questions the usefulness of systematic MRI screening for OPG diagnosis. Conversely, this study suggests that the indication of neuroimaging should be dictated by the results of annual clinical and ophthalmological assessments.

1. Introduction

Neurofibromatosis type 1 (NF1) is a multisystemic, inherited, autosomal dominant disorder with an estimated prevalence of 1 in 3500.¹ The gene of this neurocutaneous disorder, a tumor suppressor gene, was cloned on the long arm of chromosome 17 (17q11.2) in 1990. The diagnostic criteria for NF1 are clinical, established on a National Institutes of Health consensus in 1987,² re-evaluated in 1997. NF1 prognosis remains unpredictable, with the possibility of complications affecting various organs. One of the most common tumors in patients with NF1 is optic pathway glioma (OPG). It occurs mainly in childhood under six years of age with an estimated frequency of 15%–20% in NF1 children revealed by systematic neuroimaging (MRI).^{3,4} Despite the high frequency of the tumor in this population, routine MRI screening has not been recommended in asymptomatic NF1 children.⁵ This recommendation is based on a longitudinal study³ showing that the majority of OPGs detected are asymptomatic without radiological progression, the fact that MRI cannot differentiate progressive and non-progressive forms of OPG, and finally no clear evidence exists to show that earlier intervention changes the prognosis for these patients.⁵ Conversely, the NF1 Optic Pathway Glioma Task Force recommends that all newly diagnosed NF1 patients under six years of age have full yearly ophthalmological examinations with assessment of visual acuity, visual fields, and funduscopy and slit-lamp examinations. In 2001, members of a French medical network devoted to NF1⁶ elaborated recommendations for the management of the disease. The group considered that MRI for early detection of OPG in young children should remain controversial because of the difficulty of obtaining complete and reliable ophthalmologic examinations in these children, especially in children under six years of age or in children with cognitive impairment. Accordingly, the French NF1 expert group recommended annual systematic ophthalmologic assessment in all NF1 children and systematic MRI in all newly diagnosed NF1 children under six years of age and/or in children with cognitive impairment. Twelve years after these recommendations were made, this study aimed to review the medical records of the children systematically screened by ophthalmologic and MRI examinations and to determine the influence of this screening on the therapeutic management of children with OPG.

2. Materials and methods

This multicentric retrospective study was conducted between 2001 and 2007 in six French Pediatrics Multidisciplinary Neurofibromatosis Centers (Lyon, Montpellier, Nantes, Armand Trousseau Hospital in Paris, Toulouse and Tours). All these centers followed the guidelines recommended in 2001 and published in 2002 by the French NF1 expert group.⁶ All children referred to one of these six multidisciplinary centers with a new NF1 diagnosis since January 2001 (from January 2001 to July 2007) were included in the study. The inclusions were discontinued after 2007 for two reasons: the necessity for sufficient follow-up and because after this time, MRI screening was less systematic in some centers. NF1 diagnosis was based on clinical criteria defined by the NF1 Consensus Conference.² All children under six years of age diagnosed with NF1 were screened systematically by brain and orbit MRI and ophthalmologic examination. Depending on the center, MRI was performed with or without sedation and repeated two years later if the results were normal. Ophthalmologic examinations included assessments of visual acuity, funduscopy, and slit-lamp examinations.

The data reviewed from medical records were age at NF1 diagnosis, age at OPG diagnosis, NF1 characteristics (sporadic or familial form, clinical manifestations, etc.), ophthalmologic screening results, and brain and orbit MRI results with location of the tumor. OPG is defined on MRI by an enlarged T1 isointense optic nerve with a T2 hyperintense signal with variable gadolinium enhancement. MRI provides assessment of the posterior extent of the tumor. We differentiated groups of children according to the MRI results as children with OPG and without OPG. For the group of children without OPG at the first examination, we recorded the annual examination and determined if they had been given a second MRI. In the OPG group, children were classified according to their status as either being asymptomatic or initially symptomatic. The asymptomatic OPG group represented children who had had a “baseline” MRI performed as a screening tool. In the symptomatic OPG group, patients had brain MRI to investigate a specific clinical sign (neurologic, ophthalmologic, or endocrinologic) that could be attributed to the presence of OPG. We reviewed the successive ophthalmologic and MRI examinations (studies at three-to six-month intervals, the first 12

months, and then yearly). A decrease in visual acuity or the appearance of endocrinologic symptoms related to the tumor were considered as clinical OPG progression. Visual function impairment was defined as a visual loss of two degrees. We considered that visual deficit was severe when visual acuity was less than 2/10 and mild when visual acuity was between 2/10 and 8/10 and/or when the visual field was altered. Increase of tumor volume on MRI studies was considered as radiological progression.

We compared asymptomatic and symptomatic groups: mean values or medians were used as continuous variables and frequencies were used as categorical variables. Non-parametric tests were used to compare continuous variables and the Pearson's chi-squared test for categorical variables; the level significance corresponded to a value of $p < 0.05$.

3. Results

3.1. All groups

The study was conducted from January 2001 to July 2007 and included 306 newly diagnosed children screened with systematic MRI in the five different centers. OPG was identified by MRI in 45 children (14.7%), which included 36 (80%) asymptomatic and nine (20%) symptomatic children at the time of diagnosis. Two children with a normal first MRI developed symptomatic OPG subsequently. The general characteristics of the population are summarized in [Table 1](#). The average age at NF1 diagnosis was three years, the sex ratio was 1:1, and 42% had a family history of NF1. When the first MRI screening was normal, a second MRI was performed two years later in 45 children, which was normal in all cases. The first MRI was performed before the age of three years in 47% of case. The average age at OPG diagnosis was 3.4 years with six patients (13%) diagnosed after the age of six years. Among these patients, only one girl was symptomatic. She was lost to follow-up. Of the 45 OPG patients, 20 patients (44%) had isolated optic nerve involvement of one or both nerves, 16 (35%) had both nerve and chiasma involvement, and six (13%) had isolated chiasma enlargement. Only three patients (7%) had post-chiasmal extension. Four OPG patients had other CNS lesions. The MRI results were consistent with two cerebellar pilocytic astrocytomas and two non-evolutive pontine gliomas. Nine patients were symptomatic at the time of MRI screening: almost all the children with symptomatic OPG had isolated or associated ophthalmologic symptoms – strabismus was recorded in five cases, decreased visual acuity in

Table 2 – Comparison evolution for asymptomatic and symptomatic GVO Groups.

	Asymptomatic (n = 36)	Symptomatic (n = 9)	P value
Median age at time for OPG diagnostic (y)	2.8	3.3	0.117 ^b
Location n (%)			0.816 ^a
Nerve only	17 (47%)	3 (33%)	
Chiasma only	5 (14%)	1 (11%)	
Nerve + Chiasma	12 (33%)	4 (44%)	
Nerve + Chiasma + RC	2 (5%)	1 (11%)	
OPG = Optic Pathway Gliomas; y = years; RC = retro chiasmatic location.			
^a Test Khi-2 of Pearson.			
^b non parametric test.			

three cases, papillary abnormalities in one case, and proptosis in one case. Five (5/45) patients had evidence of optic disc atrophy or swelling on examination.

3.2. Symptomatic versus asymptomatic OPG at diagnosis ([Table 2](#))

The symptomatic group had a higher proportion of patients with a positive family history; however, the difference was not statistically significant. Average age at diagnosis for asymptomatic children was 3.4 years (median = 2.8) and 3.5 years (median = 3.3) for symptomatic children. This difference in age of diagnosis between the two groups was not statistically significant. The asymptomatic group had a higher proportion of patients with isolated optic nerve involvement (47% vs. 33%), whereas the symptomatic group had a higher proportion of patients with both chiasmatic and nerve involvement (44% vs. 33%); however, the difference between the groups was not statistically significant.

3.3. Evolution of the two groups ([Table 3](#), [Fig. 1](#))

One symptomatic OPG patient did not return for ophthalmologic or MRI assessment and was lost to follow-up. Longitudinal data averaged 7.8 years for asymptomatic patients (range 0.8–11.8 years) and 7.7 years for symptomatic patients (range 5.3–10 years). [Table 3](#) and [Fig. 1](#) summarize the evolution in both groups. Progression was observed in 16 cases. Radiological progression without clinical progression was observed in only one symptomatic patient. Clinical progression with or without radiographic progression was observed

Table 1 – General characteristics of the population.

	Total population	Children with OPG		
		Asymptomatic	Symptomatic	Total
Number	306	36	9	45 (14,7%)
Age (mean) for NF1 diagnostic	3y	3.3y	3.7y	3.4y
Sex ratio (M/F)	158/148	17/19	6/3	23/22
Age (mean) at screening	3.4y	3.4y	3.5y	3.4y
Family history of NF1 n (%)	128 (41.8%)	14 (38.8%)	5 (55.5%)	19 (42.2%)

OPG = Optic Pathway Gliomas; M/F = Male/female; y = years; n = Number.

Table 3 — Evolution for asymptomatic and symptomatic groups.

	Asymptomatic (n = 36)	Symptomatic (n = 8)	P value
Follow-up duration (y)	7,8	7,7	0.750 ^b
Evolution n (%)			0.119 ^a
No progression	25 (69.4%)	3 (33.3%)	
Radiologic tumor progression only	0	1 (11.1%)	
Clinical tumor progression (with or without radiologic progression)	11 (30.5%)	4 (44.4%)	
Visual function at the end of follow-up n (%)			0.004 ^a
Normal	29 (80.5%)	2 (25%)	
Abnormal (Mild)	4 (11.1%)	3 (37.5%)	
Abnormal (Severe)	3 (8.3%)	3 (37.5%)	

y = years.
^a Test Khi-2 of Pearson.
^b Non parametric test.

in 15 cases (11 in the asymptomatic OPG group and four in the symptomatic OPG group). Eleven patients had ophthalmologic signs, seven had decreased visual acuity, five had visual field alteration, and four patients had endocrinologic signs (precocious puberty). One patient had visual field restriction associated with precocious puberty. Six patients with decreased visual acuity underwent chemotherapy. According to the BBSFOP regimen, Carboplatine, Natulan, Etoposide, Cisplatin, Vincristine, and Endoxan agents were used as first-line chemotherapy before 2004. According to the LGG regimen, the Carboplatine and Vincristine combination was used as first-line chemotherapy after 2004. One boy experienced a dramatic evolution. Positive maternal family history and multiple café au lait spots confirmed an NF1 diagnosis at the age of four months. At the age of 18 months, he presented right eye strabismus, visual acuity decline, visual field alteration, and pupillary afferent deficit. The MRI showed right optic nerve and chiasmatic involvement. He was referred to neuro-oncologists and underwent seven BBSFOP regimens. Despite first-line chemotherapy, serial imaging revealed right

Fig. 1 — Flow chart of the study population.

temporal and brainstem involvement, with hydrocephaly. Temodal was initiated as palliative therapy and a ventriculoperitoneal shunt was placed. This patient was tetraparetic and blind. At the end of follow-up, 31 patients (70%) had normal visual function, including 29 in the asymptomatic group and two in the symptomatic group. Thirteen patients (30%) had mild to severe visual impairment, including seven in the asymptomatic group and six in the symptomatic group. The difference between the two groups was statistically significant (Table 3). All the patients treated with chemotherapy had severe visual outcome. No difference was observed in these patients for visual function at the beginning and at the end of treatment. One patient improved the Visual Evoked Potentials without improvement of visual functions. Details for the 13 patients with abnormal visual function at the end of follow-up are described in Table 4.

4. Discussion

This study confirmed the existing epidemiologic data on OPG in NF1 in the French population, which have already been reported in American populations⁷⁻⁹: OPG concerned about 15% of NF1 children screened with MRI, a small proportion were symptomatic (around 3% of NF1 children at the time of diagnosis and 5% during follow-up), and the preponderance in females reported by others authors^{5,9,10} was not observed in our study, which revealed a sex ratio close to 1:1. The average age at OPG diagnosis was nearly 3 years, as reported in previous studies with systematic MRI screening,^{4,11} which two years earlier than the age at diagnosis reported in large retrospective OPG studies of NF1 populations without systematic MRI screening.¹² Thus, systematic MRI screening probably provides earlier OPG diagnosis.

Ophthalmologic signs were more frequent at the time of OPG diagnosis. The three most frequent ophthalmologic symptoms were decreased visual acuity (3), evidence of optic atrophy or swelling on funduscopy examination (2), or proptosis (1). One patient underwent imaging to investigate macrocephaly and one other had growth rate acceleration. King et al. (2003)¹³ reported precocious puberty in 20% of patients and poor weight gain in 4% of children with NF1 and OPG. In this study, four patients (9%) with chiasmatic involvement experienced precocious puberty during the course of OPG. When one of these symptoms was present, MRI revealed OPG in more than 50% of cases. In our study, of the six patients treated with chemotherapy, five had chiasmatic involvement, which confirms that patients with chiasmatic involvement seem to be more susceptible to visual morbidity.^{9,11,14}

Negative MRI does not rule out later emergence of OPG, as reported by other authors^{15,16}: two children presented symptomatic OPG after a first normal MRI. Moreover, newly diagnosed OPG may raise parental anxiety while most of the patients with incidentally discovered OPG will not experience any progression. These two points constitute arguments against systematic screening.

OPG progression after diagnosis was observed in 34% and more frequently in the symptomatic group; this is consistent with data published by other authors.¹⁷ Nevertheless, OPG progression in the asymptomatic group (30%) was more

Table 4 – Abnormal visual outcome at the end of the follow-up.

	Sex	Age at diagnosis (m)	Follow-up (m)	Group	OPG location	Progression	Treatment	Evolution with chemotherapy	Final outcome
1	F	76	114	AS	NO	Yes	No		Mild (VA 6/10 RE & 8/10 LE)
2	F	40	64	S	NO	No	No		Severe (Blindness RE)
3	F	29	113	AS	NO + C + OR	Yes	No		Severe (VA < 2/10 RE & Alteration VF & OA)
4	F	14	142	AS	NO + C	Yes	Yes	Stability visual function but Improvement VEP	Severe (light perception RE)
5	M	14	108	AS	NO + C	Yes	Yes	further visual degradation	Severe (VA < 2/10 RE&LE)
6	M	21	105	AS	NO	Yes	No		Mild (VA = 5/10 LE + Palor ON)
7	M	69	89	AS	NO	Yes	No		Mild (Alteration VF)
8	M	18	100	S	NO + C	Yes	Yes	further visual degradation	Severe (Bilateral blindness)
9	M	40	100	S	NO + C + OR	Yes	No		Mild (Alteration VF)
10	F	18	92	AS	NO + C	Yes	Yes	further visual degradation	Mild (Alteration VF & OA)
11	M	45	72	S	NO + C	Yes	No		Mild (VA = 6/10 RE & LE)
12	M	18	120	S	C	Yes	Yes	further visual degradation	Severe (Bilateral blindness)
13	M	51	120	S	NO	No	Yes	Stability visual function	Mild (OA RE + Oculomotor palsy)

M = Male; F = female; m = months; AS = asymptomatic; S = symptomatic; OPG = Optic Pathway Gliomas; NO = Optic Nerve; C = Chiasma; OR = optic radiations; VA = Visual Acuity; VF = Visual Field; RE = Right Eye; LE = Left Eye; OA = optic atrophy.

frequent than reported previously.³ However, clinical or radiological changes and real tumor progression were not correlated. Serial changes in visual function do not reliably detect tumor progression and conversely, radiological evidence of tumor progression does not reliably correlate with changes of visual function.¹⁸

At the end of follow-up, visual impairment concerned 30% of the children, which corresponds to other reports (22%–31%) on more recent series.^{4,12,13} The percentage of children with visual impairment (mild or severe) at follow-up was significantly higher in the symptomatic group (6/8) compared to the asymptomatic group (7/36). Thiagalingam et al.¹² reported 16.7% of patients having moderate to severe bilateral impairment. In the Blazo and Thiagalingam studies, patients systematically screened at OPG diagnosis did not have severe visual impairment at follow-up. Fisher et al. (2012)¹⁷ reported poorer prognosis when OPG involved posterior optic tracts: our study did not reveal differences in tumor location between the groups.

The range of visual acuity tests used on our patients at the different centers was a weak point in our study and highlights the difficulty of assessing visual function accurately in young children. The Response Evaluation in Neurofibromatosis and Schwannomatosis Visual Outcomes Committee recently defined visual function assessments using consistent quantitative testing methods as the best functional outcome measures for NF1-OPG clinical trials. Teller acuity cards are recommended for use as a primary visual acuity endpoint and HOTV as a secondary endpoint once subjects are old enough to complete it. They also propose evaluating visual quality of life using the Children's Visual Function Questionnaire as a secondary endpoint.¹⁹

Most patient conditions were managed conservatively (87%). Six children (13%) were treated with chemotherapy because of worsening visual function. All of these children had severe or mild visual impairment at the end of follow-up. In four children, visual function worsened despite chemotherapy and none had improved function. As mentioned by some authors,¹⁸ it is still unknown whether this worsening during chemotherapy reflects progression of the illness or damage occurring prior to treatment. Nevertheless, limited data exist regarding the clinical outcome of children with OPG after chemotherapy.²⁰ Moreno et al. reviewed the literature systematically from 1990 to 2008 and reported the visual outcome in children with OPG who received chemotherapy. Of 85 potentially relevant publications, only eight were included. Dalla Via et al. (2007)²¹ described unsatisfactory visual outcome in children with NF1 and OPG treated by chemotherapy. Fisher et al.¹⁷ reported a retrospective multicenter study including 115 patients. Eighty-eight subjects and 168 eyes were evaluated for visual acuity outcome. After chemotherapy, 32% of children improved, 40% remained stable, and 28% worsened. The lack of correlation between visual and radiographic outcomes in this study argues against the use of MRI response as the gold standard of treatment for this tumor. Kalin-Hajdu et al.²² recently reported decreased visual acuity in seven NF1-OPG patients directly after chemotherapy and at long-term follow-up. Whether chemotherapy, when initiated due to a slight decline in visual function, is superior to conservative management needs to be demonstrated in NF1 children through a prospective, multicenter randomized study.

In conclusion, our multicenter study does not support a clear benefit of systematic MRI screening in NF1 children under six years of age. Firstly, systematic neuroimaging in our study did not influence the therapeutic management of OPG patients since decreased visual acuity was the primary reason for initiating treatment. Secondly, while the OPG diagnosis was made early, treatment by chemotherapy did not improved the final visual outcome; this conclusion is in accordance with several studies questioning the efficacy of chemotherapy in children with NF1 and OPG. Thirdly, the majority of NF1 children who developed OPG did not require treatment and only children who had progressive visual deterioration needed treatment. To date, the best method of treatment has not been determined and probably new therapies targeting mTOR activity should be developed for treatment of tumors in NF1 patients. Finally, our study suggests that brain MRI should be dictated by the results of systematic annual, clinical and ophthalmological examinations.²³ In this case, abnormal eye examinations or precocious puberty should lead to an investigation of OPG by MRI.²⁴ We must remain cautious, of course: the examination should be complete and beyond doubt. In light of these results, the French recommendations on the follow-up of children with NF1 should be reviewed.

Conflict of interest

The authors declare no conflict of interest.

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