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Original article

Brain gliomas, hydrocephalus and idiopathic aqueduct stenosis in children with neurofibromatosis type 1

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Abstract

Purpose: To evaluate the incidence and clinical importance of brain gliomas – optic pathway gliomas (OPGs) and especially gliomas outside the optic pathway (GOOP) for children with neurofibromatosis type 1 (NF1), additionally, to assess the causes of obstructive hydrocephalus in NF1 children with an emphasis on cases caused by idiopathic aqueduct stenosis.

Subjects and methods: We analysed data from 285 NF1 children followed up on our department from 1990 to 2010 by the same examination battery.

Results: We have found OPGs in 77/285 (27%) children and GOOPs in 29/285 (10,2%) of NF1 children, of who 19 had OPG and GOOP together, so the total number of brain glioma was 87/285 (30,5%). GOOPs were significantly more often treated than OPGs ($p > 0.01$). OPGs contain clinically important subgroup of 14/285 (4.9%) spreading to hypothalamus. Spontaneous regression was documented in 4/285 (1.4%) gliomas and the same number of NF1 children died due to gliomas.

Obstructive hydrocephalus was found in 22/285 (7.7%) patients and 14/22 cases were due to glioma. Idiopathic aqueduct stenosis caused hydrocephalus in 6/22 cases and was found in 2.1% of NF1 children. Two had other cause.

Conclusions: The total brain glioma number (OPGs and only GOOPs together) better reflected the overall brain tumour risk for NF1 children. However, GOOPs occur less frequently than OPGs, they are more clinically relevant. The obstructive hydrocephalus was severe and featuring frequent complication, especially those with GOOP. Idiopathic aqueduct stenosis shows an unpredictable cause of hydrocephalus in comparison with glioma and is another reason for careful neurologic follow up.

Keywords: Neurofibromatosis type 1; Optic pathway glioma; Brain glioma; Hydrocephalus; Idiopathic aqueduct stenosis

Abbreviations: D2+H, Dodge 2 with hypothalamus involvement; ETV, endoscopic third ventriculostomy; FASI, Focal Areas of Signal Intensity; GOOP, Glioma Outside Optic Pathway; NF1, Neurofibromatosis Type 1; OPG, Optic Pathway Glioma; VPS, Ventriculoperitoneal shunt

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1. Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder, with complete penetrance, variable expression and a high rate of new mutations. The incidence is about 1: 2500–3000 individuals, the average global prevalence 1 case per 3000 individuals [1]. The NF1 gene is located on the 17th chromosome (17q11.2) and encodes neurofibromin. Neurofibromin is known as a tumour suppressor and NF1 patients are at increased risk for developing benign and malignant tumours.

The diagnosis is based on the National Institutes of Health (NIH) Diagnostic Criteria for Neurofibromatosis Type 1 [2].

The most common NF1 brain gliomas are optic pathway gliomas (OPG), usually with a presented incidence of 15–20%, but in fact incidence differs between studies from 4.8% to 29% [3,4]. The period of OPG manifestation is mostly up to six years of age, respectively during first decade of life, but later manifestations have been noted, too, and OPG appearing in older children or adults could be more aggressive and more often progress than in small children [5,6]. Histologically they are usually pilocytic astrocytomas grade I, they are in one half to two thirds asymptomatic, and their biologic potential is more favourable with a better prognosis than in non-NF1 patients [7,8]. Identifying which lesions will become aggressive is unpredictable in the beginning and also spontaneous regression is described [8]. The most common OPG symptoms are ophthalmological, such as vision loss or squinting, but also pubertas praecox or small linear growth could appear too. According to Listernick et al., the actual incidence of symptomatic OPGs in NF1 is probably 1.5–7.5% [9]. OPG are classified according to modified Dodge criteria from 2008 into four types involving: type 1 – optic nerve/s, type 2 – chiasma, type 3 – optic tracts and type 4 – posterior tracts. H+/− means hypothalamus involvement and LM +/− leptomeningeal dissemination. According to Taylor et al., 98% of OPG involve the optic nerve – one or both, and/or optic chiasma [10]. The MRI definition of the OPG is an enlargement of the optic nerve beyond normal size, with or without contrast enhancement on brain MR imaging [8].

Gliomas outside the optic pathway (GOOPs) in NF1 children are less commonly mentioned in literature, and the incidence rate is not really known. Their biologic potential, in comparison with non NF1 patient with brain gliomas, is often less aggressive, but in comparison with OPG it is more important in NF1 patients. The described localisation is mostly in the brainstem and cerebellum [5,11,12]. GOOPs have sometimes difficult differential diagnosis with distinguishing from hyperintense lesions on T2W images typical for NF1. These findings are called Focal Areas of Signal Intensity (FASI) [13]; they appear typically at about three years of age, increase in number and size into adolescence, and then spontaneously regress. They are typically hyperintense on T2W and FLAIR MR images and iso- to mildly hypointense on T1W images. Sometimes they show slight T1 shortening, which has been related to myelin clumping or microcalcification. Mass effect, vasogenic oedema, and contrast enhancement are characteristically absent [14], however, the lesions in the globus pallidus occasionally have a mild mass effect and may be bright on T1W images [15]. The incidence of FASI in the Czech NF1 child population is 86% [16].

Obstructive hydrocephalus is mostly caused by an expansive lesion compressing the liquor pathway - especially a chiasmatic, hypothalamic, or brainstem tumour. The incidence in NF1 patients is 1–5% [4,11,17,18].

Idiopathic aqueduct stenosis of the distal part of the aqueduct is a rare condition connected with NF1 and also another possible cause of obstructive hydrocephalus in NF1. Incidence is described in about 1.5–2% of NF1 patients and the aetiology is unknown [11,12,18]. Phase-contrast MR imaging is helpful for the diagnosis of aqueduct stenosis [19]. Clinical signs of increased intracranial pressure from this condition are usually very inconspicuous, although patients could have huge findings on brain imaging.

2. Subjects and methods

We undertook a retrospective analysis of 285 NF1 children according to the NIH diagnostic criteria for NF1, followed up at the Department of Paediatric Neurology in Motol Hospital (which is University Hospital of Second Medical School of Charles University in Prague), between 1990 and 2010. This department examined patients from the whole Czech Republic. Records were collected for 154/285 (54%) boys and 131/285 (46%) girls, ranging in age from birth to their nineteenth birthday. The cohort contains children followed up at our Department, evaluated by the same scheme – neurologic and ophthalmologic examinations, and all had also at least one brain MR imaging. Children without brain MR imaging (none or only CT) or with lack of clinical information were excluded from the study. Neurologic examination contained evaluation of muscle tonus, cranial nerves function, deep tendon reflexes, cerebellar function, in nursling evaluation of psychomotor development, annually during follow up, at least once, and in patients with neurologic symptoms/problems as frequently as needed. Opthalmological evaluation included visual acuity since 3 years old and evaluation of optic disc (swelling or atrophy) each 4–6 months, in cooperative children color vision and perimeter once a year. – Some brain MRI examinations were recorded on a 0.5 T machine (14 patients) and the main part of the cohort (271 patients) on 1.5 T MR equipment. Brain MRI protocol contain T1W, T2W and FLAIR imaging,

coronal sequences for optic nerves evaluation, sagital sequences, and imaging after contrast application. All findings were evaluated at the Department of Radiology in Motol Hospital and described by paediatric radiologists on MRIs with the same OPG diagnostic criteria. Problematic findings, especially in identifying FASI and suspected GOOP, were discussed on multidisciplinary seminars with paediatric specialists: neurologists, neurosurgeons, radiologists and oncologists.

The aim of the study was to emphasis especially GOOPs and their importance for NF1 children although they has been frequently missed out or outshined by OPGs, additionally, to assess the causes of obstructive hydrocephalus in NF1 children and show the rare cases caused by idiopathic aqueduct stenosis.

2.1. Evaluated MR findings

OPGs were evaluated in all 285 NF1 patients and were classified as a dilatation of the optic nerve more than 4 mm on the coronal sequences, and in the chiasma as a widening more than 4 × 10 mm (height × width). The measurements were based on Avery et al., Karim et al., Kornreich et al. and Votruba et al. [8,20–22]. Accessory information as elongation of the optic nerve, kinking, mass effect and enhancement after contrast administration were also described. The tumour localisation was defined according to MRI modified Dodge criteria: type 1 – optic nerve/s, type 2 – chiasma, type 3 – optic tracts and type 4 – posterior tracts, H+/− means hypothalamus involvement and LM +/− leptomeningeal dissemination. [10].

GOOPs were evaluated in all 285 patients. The diagnosis of a tumour was considered in the presence of two or more of the following radiological features: expansive lesion, contrast enhancement and mass effect [5]. MRS was made in only some cases so we did not use it in the study. The histology was reviewed in available cases and classified according to the the 2016 World Health Organisation (WHO) classification of tumours of the central nervous system [23].

FASI has been defined as hyperintense on T2W and FLAIR MR images and iso- to mildly hypointense on T1W images, without mass effect or vasogenic oedema [14], however, the lesions in the globus pallidus occasionally have a mild mass effect and may be bright on T1W images [15]. They do not enhance after gadolinium administration and do not lead to focal neurological symptoms. Problematic lesions were carefully followed up and when change (and fullfit glioma definition, especially when became contrast enhancing) they were called gliomas. FASI were evaluated in 271/285 (95.1%) cases. FASI were not evaluated in 14 children with an incomplete description examined on 0.5 T MR equipment.

Obstructive hydrocephalus with its cause and idiopathic aqueduct stenosis were evaluated in all 290 patients.

2.2. Therapy

The glioma´s therapy means neurosurgery treatment, actinotherapy or chemotherapy.

Neurosurgeons made partial or total tumour resection, evaluated cystic portion and/or solved hydrocephalus, mostly by ventriculoperitoneal shunt implantation. In operated cases the histology was also available. Neurosurgeons made also biopsy in indicated cases (especially where was suspection to higher grade glioma), but this was not count as neurosurgery therapy. Actinotherapy was preferred in early 1990th, but because of side effects and serious consequences was later determinate for specific cases only. Localised actinotherapy - gamma knife was used in some patients too. Nowadays, respectively since 2000th, the chemotherapy was preferred therapy for NF1 patients with glioma, especially due to SIOP protocol for low grade gliomas (SIOP LGG 2004 protocol). Some patients needed combination of therapeutic methods. Because the therapeutic strategy subsequently changed during followed up period, we showed only the numbers of treated cases, without next specification. The therapeutic strategy was made by paediatric oncologists in cooperation with neurosurgeons in Motol Hospital.

The OPG treatment criteria were based on imaging findings – hudge OPG or progression with optahmologic problems as decrease or worsing visual acuity, optic disc atrophy and neurologic symptoms as proptosis, ocular palsy and hydrocephalus development. GOOP treatment was decided according to imaging finding but also due to clinical findings – neurologic symptoms. Neurosurgery has had still an important position in GOOPs treatment - tumour resection or hydrocephalus solution.

2.3. Statistical analysis

We compared the clinical importance in the necessity of treatment in OPG subgroups Dodge 1 and Dodge 2, and also in OPGs versus GOOPs. Differences were tested by a x^2 test, with statistically significant P-value < 0.05, and P-value < 0.01 was considered to be statistically very significant.

3. Results

We evaluated 285 NF1 children, 131 (46%) girls, 154 (54%) boys.

3.1. Optic pathway gliomas

OPGs were found in 77/285 (27%) children, 37 girls and 40 boys. We classified them according to modified Dodge criteria: 35 gliomas were Dodge 1 and 42 were Dodge 2. We did not find patients with Dodge 3 or 4 in our cohort (Table 1, Fig. 1).

OPGs Dodge 2 included 14 OPGs spreading to the hypothalamus (Dodge 2 + H). Nine of the 14 developed pubertas praecox and one had other endocrinopathy, 13/14 children had also visual problems. Only one patient in this subgroup was not treated for an OPG.

We have found three patients with well documented spontaneous OPG regression – one with Dodge 1 OPG and two had Dodge 2 OPG (none from Dodge 2 + H subgroup).

OPGs were diagnosed at the median age 6 years (72 months) old (range from birth to 19 years old).

Twenty-nine/35 Dodge 1 OPG patients were only followed up – 20/29 had unilateral OPG and 9/29 were with bilateral OPGs. Twenty-three/29 had normal visus, which got worse in only one patient, and was joined to fast worsening of the clinical state, especially due to the GOOP progression. Six/29 patient had visual problems, which were stable. Three patients had also some endocrinologic problems. Sixteen/42 Dodge 2 OPG were not treated. Forteen/16 had normal visus, 2/16 had amblyopia and visual impairment, all patients were without ophthalmologic progression during follow up. Pubertas praecox was found in 4/16 cases and one/16 was treated with grow hormone (Table 2A).

Thirty-two/77 OPGs were treated – six/35 Dodge 1 and 26/42 Dodge 2 OPGs. Four/6 Dodge 1 OPGs were unilateral gliomas, three patients had severe visual impairment and underwent neurosurgery resection of optic nerve with glioma, one patient had normal visus, and chemotherapy was indicated due to MRI progression. Two/6 patients with bilateral OPGs were treated with combination of treatment methods, because of clinical progression after first therapy. Thirteen/26 Dodge 2 OPGs were from Dodge 2 + H subgroup, and initial visus was normal in only one/13 case. Other ophthalmologic symptoms were bulbus protrusion (2 cases) and squinting (1 patient). Nine/13 children had pubertas praecox and 1/13 another endocrinopathy. Monotherapy was used in 8/13 cases, and five/13 children must be treated with combination of treatment methods. Visus was stable in 5/13 cases, in 7/13 progress and in only one/13 was little better after treatment. Two patients developed moya-moya syndrome after actinotherapy. Another 13/26 Dodge 2 OPGs were from subgroup without hypothalamus involvement. Two/13 patients had initially normal visus, but both with later progression, 11/13 patients showed decreased visus, with next progression in 3 cases, stable in 7 cases, and one patient was blind on affected eye after neurosurgery. Other ophthalmologic symptoms were: exophthalmus (1 patient), nystagmus (3 cases), squinting (1 case). Five/13 children had pubertas praecox, one mild hyperprolactinemia. Ten/13 children were threated with monotherapy, three/13 with combination (Table 2B).

Respectivelly, in conclusion, only eight symptomatic OPGs were not treated, and their ophthalmologic functions were stable during follow up. And from treated symptomatic OPGs only twelve had stable visual functions and even in one case was visus little better.

We compare the clinical importance of Dodge 1 and 2 groups statistically (according to necessity of treatment) and found statistically very significant differences with Dodge 2 being clinically more relevant than Dodge 1 OPGs ($p < 0.001$), because they more often needed treatment.

Table 1
Numbers of OPG in our cohort.

OPG	Total	F/M	Treated	Hydr.	Died	Regr.
Dodge 1	35	18/17	6	0	0	1
Left	*11*	*6/5*	*3*			*1*
Right	*13*	*5/8*	*1*			
Bilateral	*11*	*7/4*	*2*			
Dodge 2	42	19/23	26	2	1	2
Dodge 2 + H	*14*	*4/10*	*13*	*2*	*1*	
Total	77	37/40	32	2	1	3

OPG – optic pathway glioma, F/M = female/male, Hydr. = hydrocephalus, Regr. = spontaneous regression, Dodge 2 + H = Dodge 2 + hypothalamus involvement.

3.2. Gliomas outside optic pathway

GOOPs were found in 29/285 (10,2%) of NF1 patients in our cohort. We divided GOOP into three subgroups - supratentorial, infratentorial and patients with more than one GOOP (Table 3).

Supratentorial gliomas were found in nine children. Three were in the hypothalamus, without connection to the chiasma (Figs. 2A–2C), and were only followed up, while two of them spontaneously regressed – both showed contrast enhancement which distinguished them from FASI, but later the tumour regressed. The regression in one boy was of both tumours: OPG and hypothalamic GOOP. Three patients had GOOP in the thalamus, all caused hydrocephalus, although all were treated one patient died due to tumour progression. Other one patient had treated GOOP in the temporal lobe and last two patients were treated and both GOOPs caused also hydrocephalus: one was located in basal ganglia and the other in pineal gland.

Infratentorial gliomas were found in 12 children. Five children had tumours in the cerebellum – three were treated and one tumour caused hydrocephalus. Six

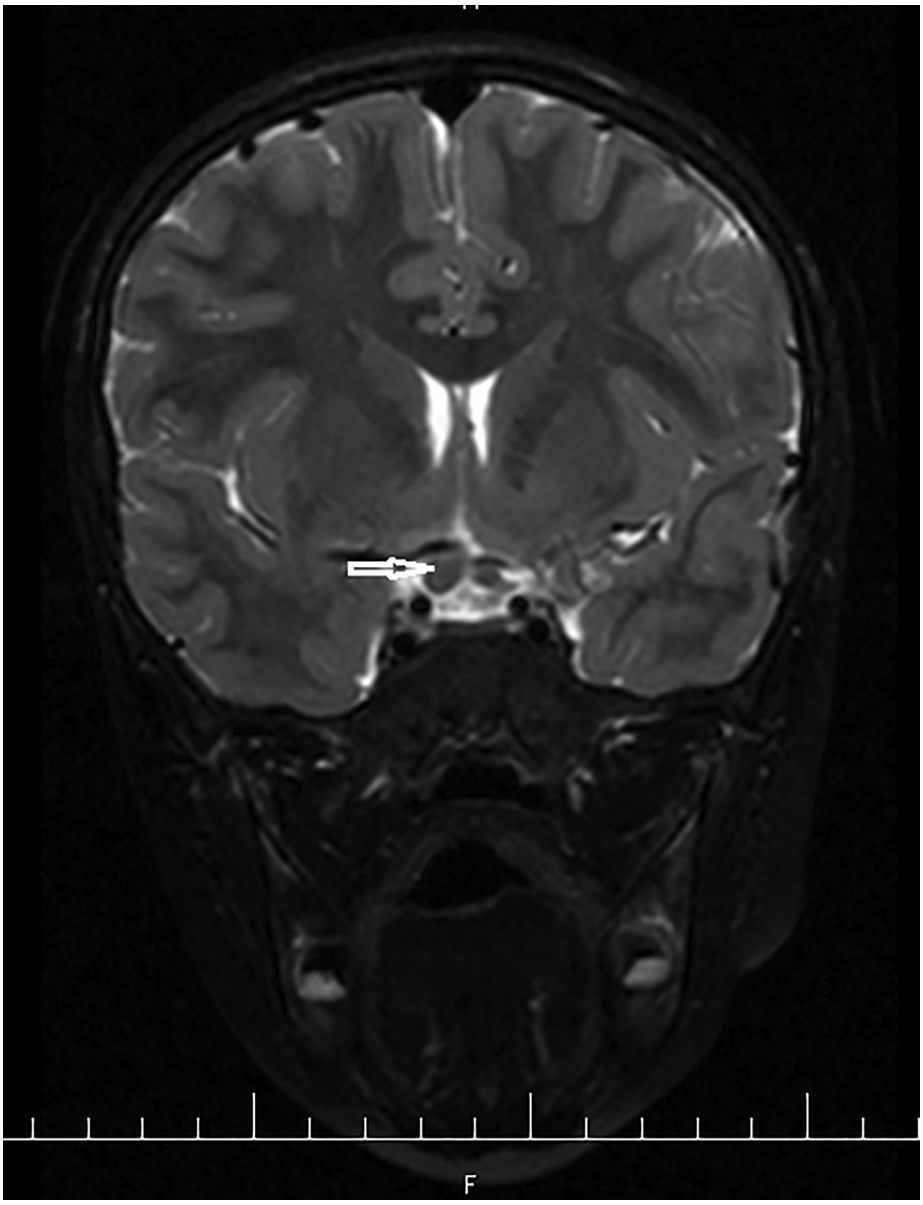

Fig. 1. Glioma of prechiasmatic part of right optic nerve (white arrow), coronal T2-TSE.F/S (T2 – weighted turbo spin echo/fat saturation) image.

tumours were located in the brainstem – two were only followed up, and four treated; one patient died. Hydrocephalus developed in three patients. One boy had a huge tumour involving the brainstem and cerebellum, and this naturally led to hydrocephalus, and this patient died due to tumour progression.

Eight children had *more than one GOOP,* and all were treated. Three patients did not have OPG together, two patients developed hydrocephalus.

The median age of GOOP discovered was 9 years and 10 months old (range from three years and three months to 18 years old). Seven/29 patients were asymptomatic, 22/29 were treated, included all with more than two GOOPs. Six patients underwent neurosurgery, one chemotherapy and four actinotherapy only. Eleven were treated by more than one modality. The histology of the available cases included astrocytomas grade I or II, only one patient had astrocytoma grade II-III.

We compared the clinical significance of GOOPs and OPGs in terms of treatment necessity and we discovered that GOOPs were clinically, significantly more important for NF1 children than OPGs ($p < 0.01$).

FASI were found in 229/271 (84.5%) cases – 106 girls and 123 boys, in the typical localisation described in NF1 patients (Figs. 3A and 3B).

Eighty-seven out of 285 (30.5%) patients had some brain glioma.

Table 2
OPGs – therapy, visual outcome.

A - only followed OPGs

Dodge classification		Initial visus		Visus during follow up		Other opthalmologicsymptoms	Endocrinologic problems
		Normal	Impairment	Stable	Progression		
Dodge 129	Unilateral OPG 20	17	3[*]	20	0	Bulbus protrusion 1	GH treatment 1 Puberta tarda 1
	Bilateral OPG 9	6	3[**]	8	1		
Dodge 216		14	2[+]	16	0		Puberta praecox 4GH treatment 1

B - treated OPGs

Dodge classification		Initial visus		Visus during follow up		Other opthalmologicsymptoms	Endocrinologic problems	Therapy			
		Normal	Impairment	Stable	Progression			NS	ActT	ChT	Multi
Dodge 16	Unilateral OPG4	1	3[§]	Amaurosis 3	1	Amaurosis after NS 3	Puberta praecox 1	3		1	
	Bilateral OPG 2	0	2[§§]	0	2						2
Dodge 226	Dodge - 2 without H13	2	11	7	5	Exophthalmus 1Nystagmus 3, Squint 1	Puberta praecox 5Hyperprolactinemia 1	2	6	2	3
	Dodge - 2 + H13	1	12	5 Better 1	7	Bulbus protrusion 2Squint 1	Puberta praecox 9Other endocrinopathy 1	1	4	3	5

GH = grow hormone, H = hypothalamus, NS = neurosurgery, ActT = actinotherapy, ChT = chemotherapy, Multi = multimodal treatment.
[*] Hypermetropia with astigmatism 1, myopia 1, decreased visus 1.
[**] Unilateral decreased visus 2, hypermetropia 1.
[+] Amblyopia and decreased visus 2.
[§] Severe visual impairment (nearly amaurosis).
[§§] Severe visual impairment.

Table 3
Numbers of GOOPs in our cohort.

GOOP	Total	F/M	Treated	Hydr.	Dead	Regr.	OPG – Dodge1	OPG – Dodge2
Supratentorial	9	6/3	6	5	1	2	1	4
Infratentorial	12	4/8	8	5	2	0	3	6
more than 1	8	3/5	8	2	0	0	3	2
- *2 or multiple GOOP*, no OPG	3	2/1	2	2				
- *multiple GOOP*, with OPG	5	1/4	5				3	2
Total	29	13/16	22	12	3	2	7	12

GOOP = glioma outside optic pathway, F/M = female/male, Hydr. = hydrocephalus, Regr. = spontaneous regression, OPG = optic pathway glioma.

3.3. Obstructive hydrocephalus

Obstructive hydrocephalus was found in 22/285 (7.7%) patients, in the median age 10 years 1 month old (range from three years and six months to 19 years old). Fourteen cases were caused by glioma, respectively two OPGs and 12 GOOPs were leading to hydrocephalus. The second most common cause was idiopathic aqueduct stenosis of distal part of aqueduct, in six patients. The other two patients had hydrocephalus: due to an expansive arachnoid cyst in one patient and secondary aqueduct stenosis (after actinotherapy) in the last one child.

3.4. Idiopathic aqueduct stenosis

Idiopathic aqueduct stenosis was found in two girls and four boys, in total 6/285 (2.1%) patients (Table 4). Only one boy had OPG and none had GOOP. The median age of manifestation was 11 years 2 months old (a range from seven years six months to 16 years 11 months). The clinical signs were very inconspicuous

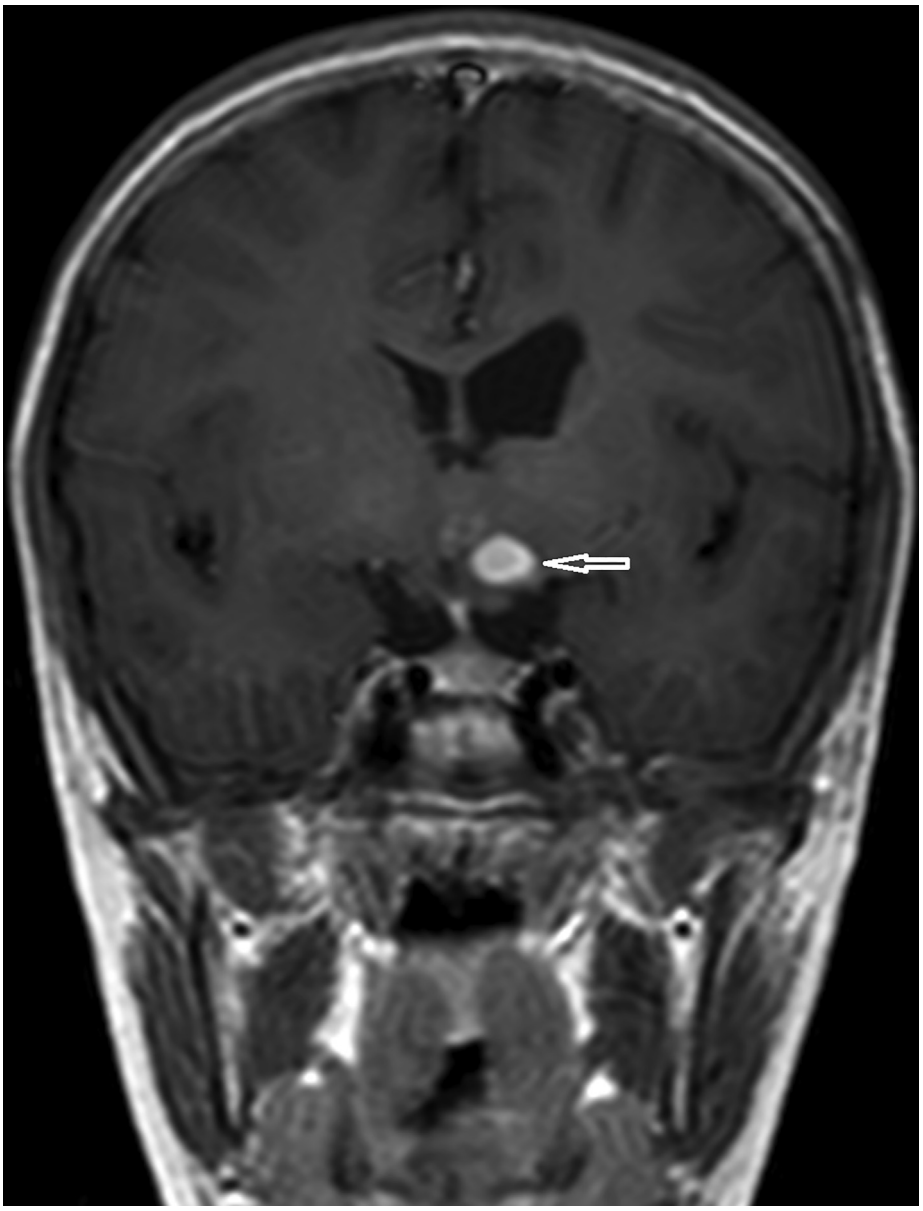

Fig. 2A. Post contrast T1/SE in coronal plane, 10 yr. girl with NF1, hypothalamic GOOP above optic chiasma enhances after Gadolinium application (white arrow).

for months and in most cases the first sign was a headache. In two cases, vomiting was irregular and attached importance to some gastrointestinal problems, similarly to an increased frequency of seizures in another one patient, which was regarded as inadequate drug therapy. In two cases, a severe impairment to speech development was described. In an asymptomatic case the hydrocephalus was found by routine MR imaging. All cases were treated; four out of six patients underwent interventriculostomy with shunt placement from the third to fourth ventricle. A ventriculoperitoneal shunt (VPS) was implanted in two out of six cases. One girl, who was asymptomatic, developed apallic syndrome after VPS implantation, which lasted for a few months and then slowly got better.

4. Discussion

NF1 is an illness with many complications, including significantly increased tumour risks and a risk of idiopathic aqueduct stenosis and development of hydrocephalus.

4.1. Optic pathway glioma

We have found 27% NF1 children with OPG in our cohort, which is higher than the commonly stated 15–20%. But, in fact, the data differs widely in literature from 4.8%, in McGaughran et al., to the highest incidence 28.6% described by Blazo et al. and 29% by Leisti [3,4,24]. The reason should be in the lack of a strictly

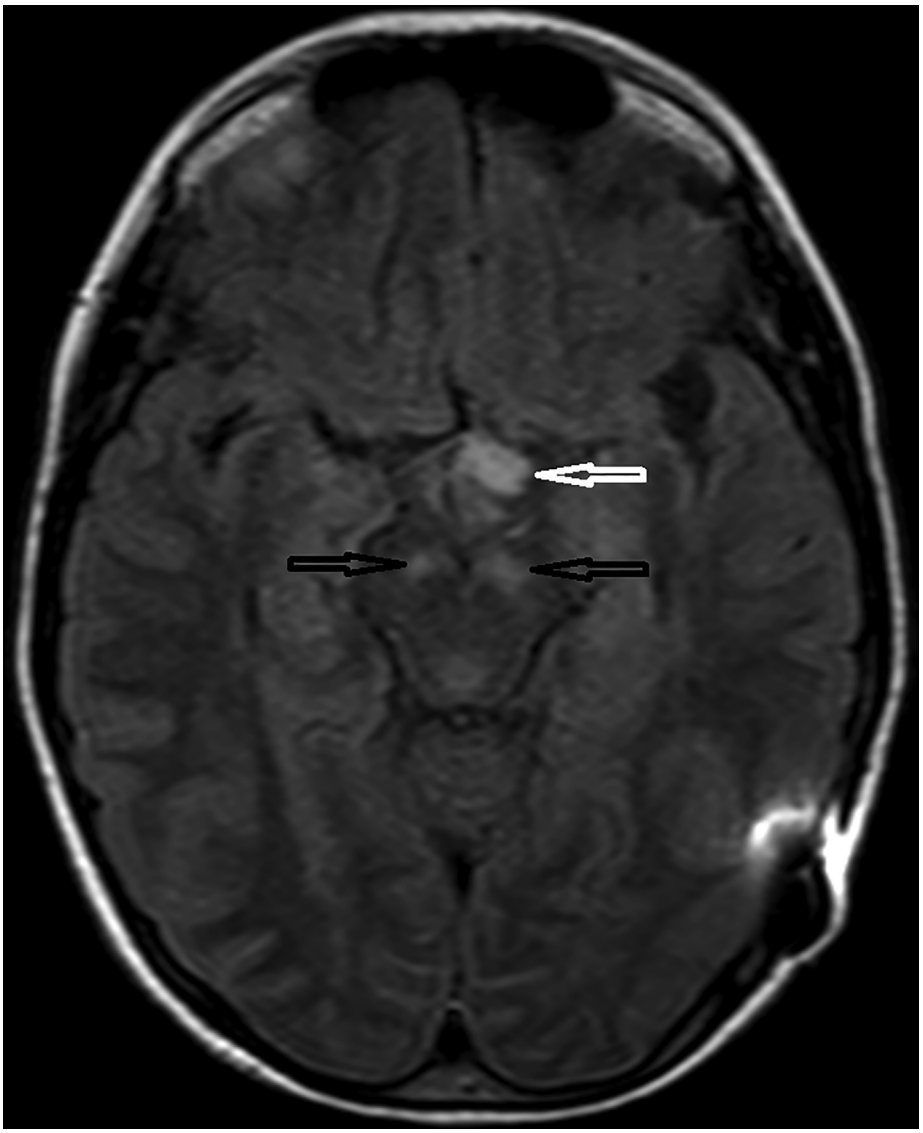

Fig. 2B. FLAIR in axial plane, hypothalamic GOOP has increased signal (white arrow), mesencephalic FASI (black arrows) have also increased signal.

defined pathology of the optic nerve and methods of cohort definition and MRI indications. We consider a normal width of the optic nerve as up to 4 mm, and enlargement above this was evaluated as glioma and the normal size of the chiasma was assessed as (height × width) 4x10 mm. But, in the literature only a few papers defined the normal optic nerve diameter. We based the limits on Avery et al. (3.9 mm), Karim et al. (a mean optic nerve diameter 3.99 ± 0.04 mm, just posterior to the globe, decreasing to 3.50 ± 0.04 mm posteriorly), and Votruba et al. (3.5 ± 0.3 mm) [20–22]. Kornreich et al. defined OPG only as an enlargement above the normal size and in chiasma greater than 1 cm [8]. The other findings (e.g., abnormal optic nerve elongation, kinking, presence of T2 hyperintensity, and enhancement after contrast administration we considered as additional data, similarly to Avery et al. [20].

The therapeutic strategy of OPGs in NF1 subsequently changed during the last thirty years, to prefer chemotherapy for OPGs and other low grade gliomas in an effort to avoid neurosurgery interventions and actinotherapy [25], and with knowledge about this mostly benign and stable disease, most of patients are only followed up on. The most jeopardised OPG subgroup is Dodge 2 + H. These patients mostly need treatment but usually had some additional clinical problems, visual or endorinological. Moreover, these tumours could also cause hydrocephalus. The treatment indica-

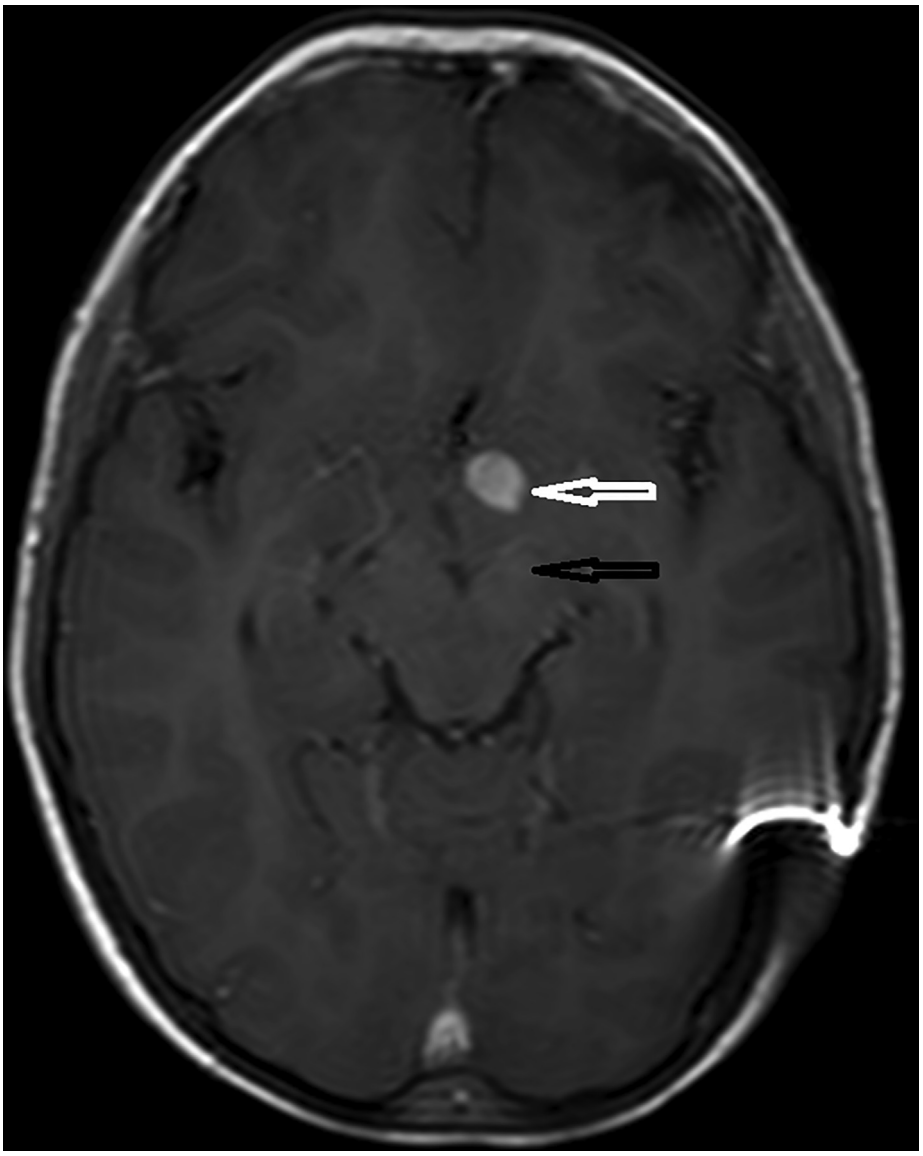

Fig. 2C. Post contrast T1/SE in axial plane, hypothalamic GOOP enhances after Gadolinium application (white arrow) contrary to unenhancing mesencephalic FASI (black arrow).

tion criteria assess not only clinical and imaging findings, but also quicknes of symptoms/findings arising and their progression.

The spontaneous regression of OPG had been described in rare cases of NF1 patients [8]. This phenomenon was described in case reports [14,26] and in followed up on in NF1 cohorts too [5,8]. Shuper et al. were the only ones noting a case of one NF1 patient with OPG regressing significantly (about 50% of volume) during follow up, but later, after 6 years, regrowth was found, and the patient had to be treated [27]. Listernick et al. and other authors evaluate the development of OPGs as unpredictable, while most OPGs remain unchanged in the long term, a smaller part progressing in size and/or clinical manifestations and a very small part of OPG spontaneously regress [9]. A similar distribution of clinical manifestations was seen in our cohort. We described spontaneous regression in 4/285 (1.4%) patients and none of these patients had glioma regrowth during next follow up. In contrast to this, the same number of patients (4/285, 1.4%) died according to tumour progression in our cohort.

4.2. Gliomas outside optic pathway

GOOPs are less commonly mentioned in literature, although they are often clinically important. Ferner et al. noted a group of gliomas outside the optic pathway, mostly located in the brainstem and cerebellum, with a frequency of 2–3% [12]. Noble et al. described four patients with GOOP from the 121 patients evaluated (3.3%), and Williams et al. reported gliomas located

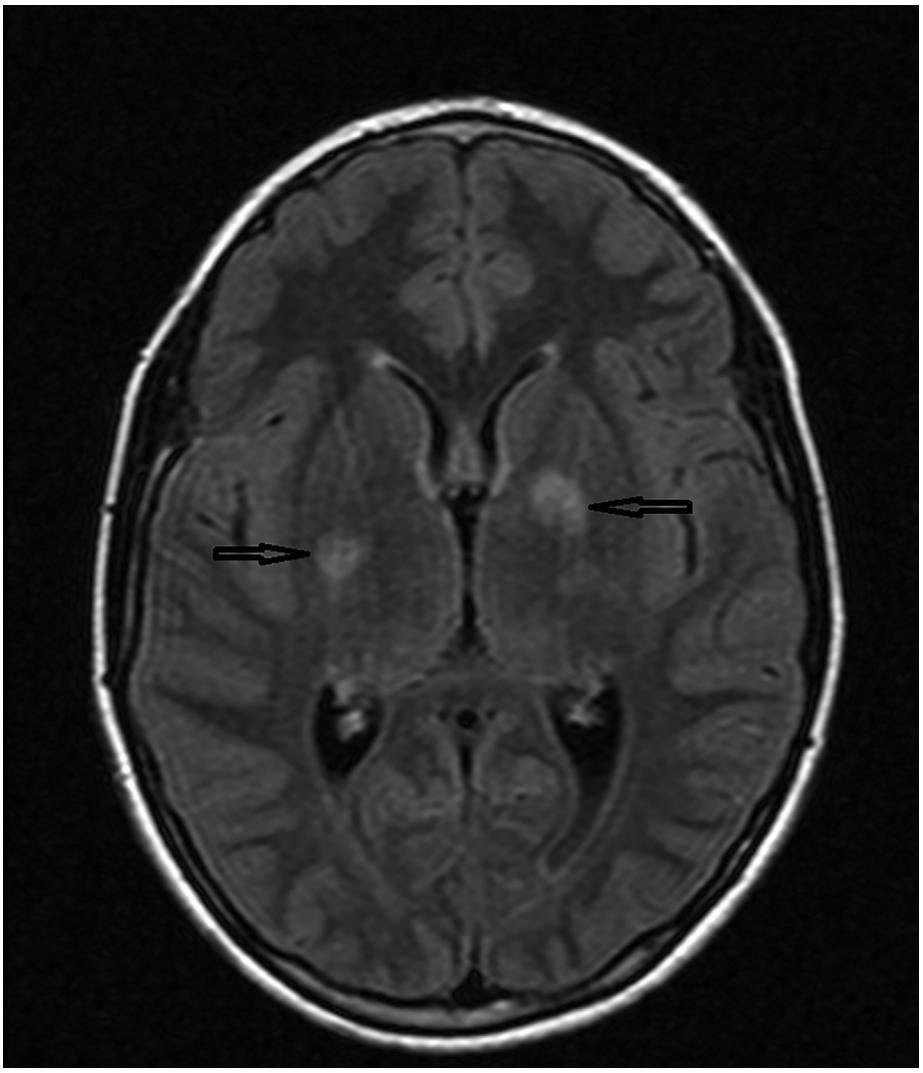

Fig. 3A. FLAIR in axial plane, 11 yr. Boy with NF1, FASI involve basal ganglia (black arrows).

in the brainstem, diencephalus and cerebellum with a frequency of 3.5% [28,29]. Blanchard et al. conducted systemic MRIs in 306 children with NF1 younger than six years old and found four patients with OPG and GOOP (4/306, 1.3%) in total [7]. We have found GOOP in 10.2% our patients. Histological findings in available cases were astrocytomas grade I or II, only one was grade II-III. The differential diagnosis of GOOP is sometimes complicated by FASI, which are the most common MR findings in NF1 children. But even in these cases histological examination is not indicated because benign character of these lesions in contrast with risks and complications contained with biopsy. These patients must be carefully long term followed up by neurologist and also MRI should be made repeatedly. Histologic examination is made in cases where neurosurgery treatment is necessary especially when hydrocephalus appears or tumour or some parts of tumour should be removed, cystic portions drained etc. A common FASI aetiology (due to NF1) appears to be a neurofibromin disorder but the mechanism has not been elucidated yet [1]. Our ambiguous cases were evaluated by paediatric radiologists and widely discussed at multidisciplinary seminars, and patients were followed up in the long-term.

Brain gliomas were found in our cohort, in total 87/285 (30.5%) NF1 children. The cumulative number of brain gliomas better expresses the overall risk of brain tumour manifestations in NF1 than the OPGs frequency alone.

4.3. Obstructive hydrocephalus

The incidence of obstructive hydrocephalus in NF1 is described as 1–5% [4,11,17,18] and tumours are the most common cause. We had a slightly higher number of obstructive hydrocephalus in our cohort, at 7.7%.

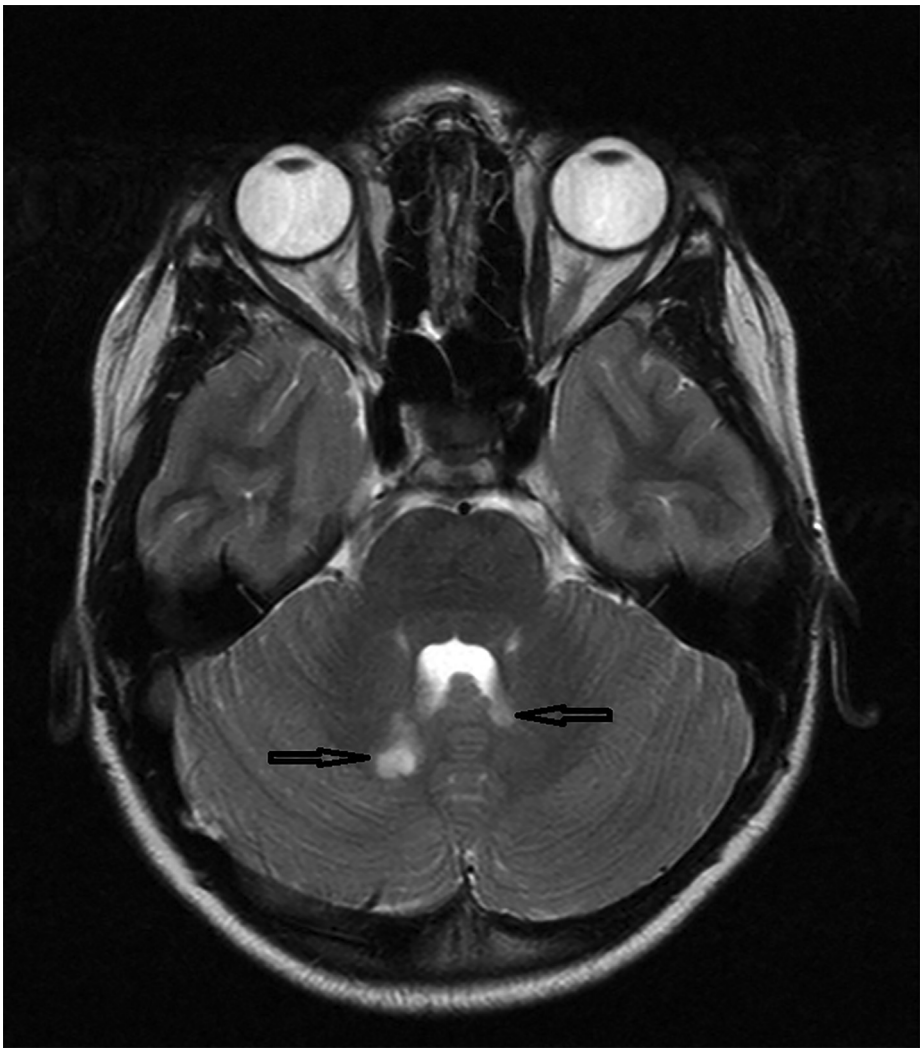

Fig. 3B. T2/TSE in axial plane, FASI involve periventicularly both cerebellar hemispheres (black arrows).

4.4. Idiopathic aqueduct stenosis

Idiopathic aqueduct stenosis of the distal part of the aqueduct is considered very rare, but for NF1 characteristics a possible cause of hydrocephalus in 1.2–2% of the NF1 patients [3,11,12]. Idiopathic aqueduct stenosis caused hydrocephalus in six out of 22, respectively six out of 285 (2.1%), of our patients. Créange et al. described four children in the evaluated group of patients with idiopathic aqueduct stenosis, and one of these patients was asymptomatic, without signs of intracranial hypertension [11]. We had also one asymptomatic patient with hydrocephalus in our cohort and the others had only inconspicuous clinical signs without significant signs of intracranial hypertension, despite a large hydrocephalus found on the brain MRI.

All NF1 patients with hydrocephalus are recommended for neurosurgery treatment – VPS implantation, interventriculostomy, or nowadays endoscopic third ventriculostomy (ETV) is preferred [11,17,30]. All of our NF1 patients with idiopathic aqueduct stenosis related hydrocephalus were treated years before ETV was available in our hospital. Nowadays, ETV is preferred to resolve hydrocephalus in NF1 children in our department.

The asymptomatic hydrocephalus in one girl with idiopathic aqueduct stenosis was found by a routine MRI examination. She developed apallic syndrome after a VPS implantation and she got better after nearly one year. The clinical course demonstrated a slow increase of intracranial hypertension with an adaptation to high intracranial pressure and subsequent risks in fast pressure compensation. Pivalliza et al. published a case report of a patient with unexpected hydrocephalus due to idiopathic aqueduct stenosis, who suddenly died at 21 years of age due to dramatic hydrocephalus decompensation just after a banal surgery performed under total anaesthesia [31]. The risk of idiopathic aqueduct stenosis is one of the other reasons for a carefull neurologic follow up and one of indication of brain imaging.

Table 4
Patients with idiopathic aqueduct stenosis and clinical signs of hydrocephalus.

Patient No.	Gender	Sign of hydrocephalus	Years of age at time of hydrocephalus finding	Therapy	Other clinical data
1	F	Asymptomatic	16 y 11 m	VPS	apallic syndrome after shunt implantation
2	F	Headache	7 y 6 m	Interventriculostomy	severe speech development impairment, mild mental retardation
3	M	Increased seizure frequency, left side hemiparesis, bilateral abducens palsy	8 y 2 m	VPS	seizures since 3 years, speech development impairment, mild mental retardation
4	M	Headache, intermittent vomiting for long time	8 y 9 m	interventriculostomy	aortal stenosis - cardiology follow up since 3 month of age
5	M	Headache, vomiting	13 y 6 m	interventriculostomy	no other clinical problems
6	M	Headache	15 y 6 m	interventriculostomy	mild mental retardation

F = female, M = male, VPS = ventriculoperitoneal shunt, y = years, m = months.

5. Conclusion

The prevalence of OPGs in our cohort was 27%. The most important was the Dodge 2 + H subgroup, but generally the clinical course of OPGs is unpredictable, with the possibility of spontaneous regression but also dramatic deterioration. GOOPs were found in 10.2% of our patients, in median age 9 years 10 months old (range from three years and three months to 18 years old), and they proved to be a higher risk for NF1 patients, more often needing treatment and potentially leading also to hydrocephalus. The total brain glioma number (OPGs and only GOOPs together) better reflected the overall brain tumour risk for NF1 children. We would like to emphasise the 7.7% total occurrence of obstructive hydrocephalus and 2.1% prevalence of obstructive hydrocephalus due to idiopathic aqueduct stenosis in NF1 children. The clinical signs of hydrocephalus according to idiopathic aqueduct stenosis were inconspicious and the development of hydrocephalus was unpredictable in comparison with hydrocephalus due to tumour. The risk of developing hydrocephalus according to idiopathic aqueduct stenosis is another possibility to carefully follow up on in NF1 children.

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Conflict of interest

All the authors claim no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.04.003.

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