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.

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

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 $\times$ 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).

Respectively, 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.

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

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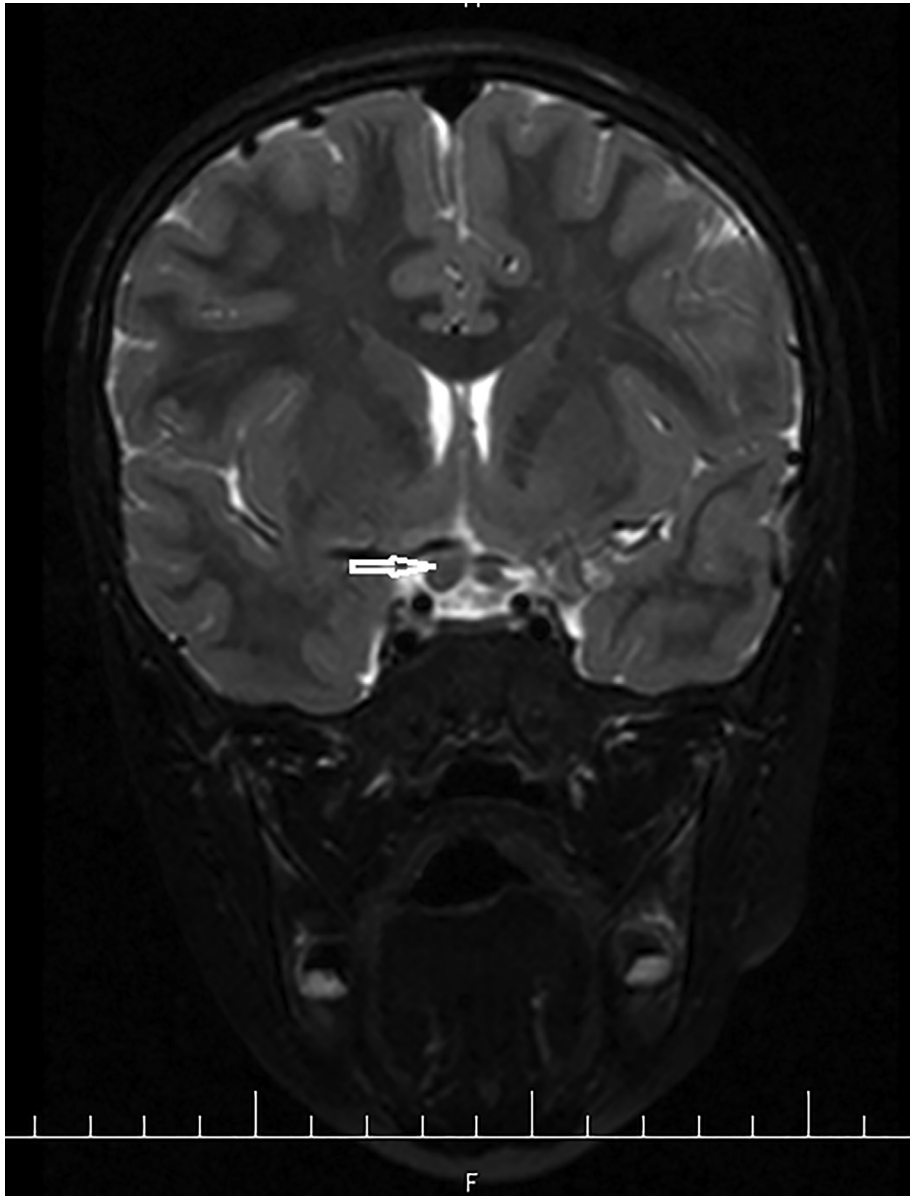
Fig. 1. Glioma of prechiasmatic part of right optic nerve (white arrow), coronal T2-TSE.F/S (T2 – weighted turbo spin echo/fat saturation) image.

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 neuro-

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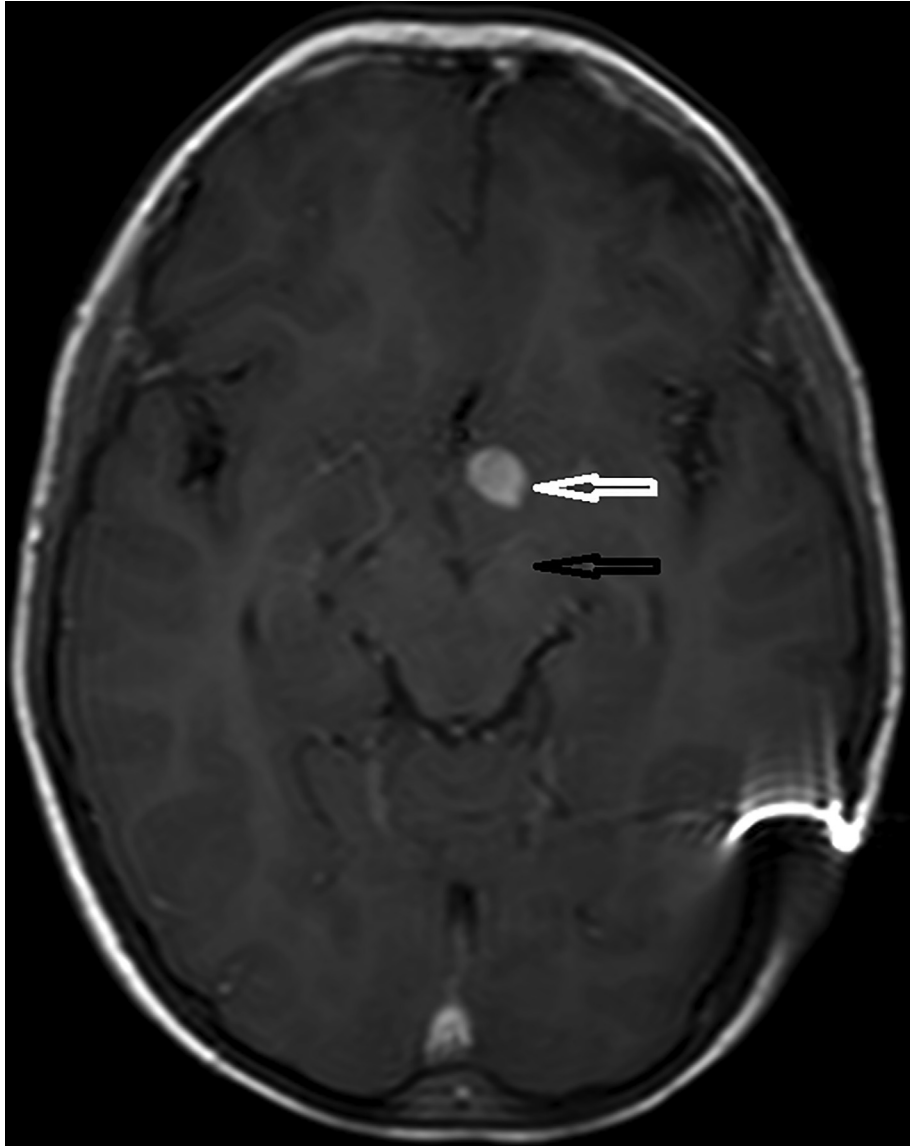
Fig. 2C. Post contrast T1/SE in axial plane, hypothalamic GOOP enhances after Gadolinium application (white arrow) contrary to unenhancing mesencephalic FASI (black arrow).

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 distri-

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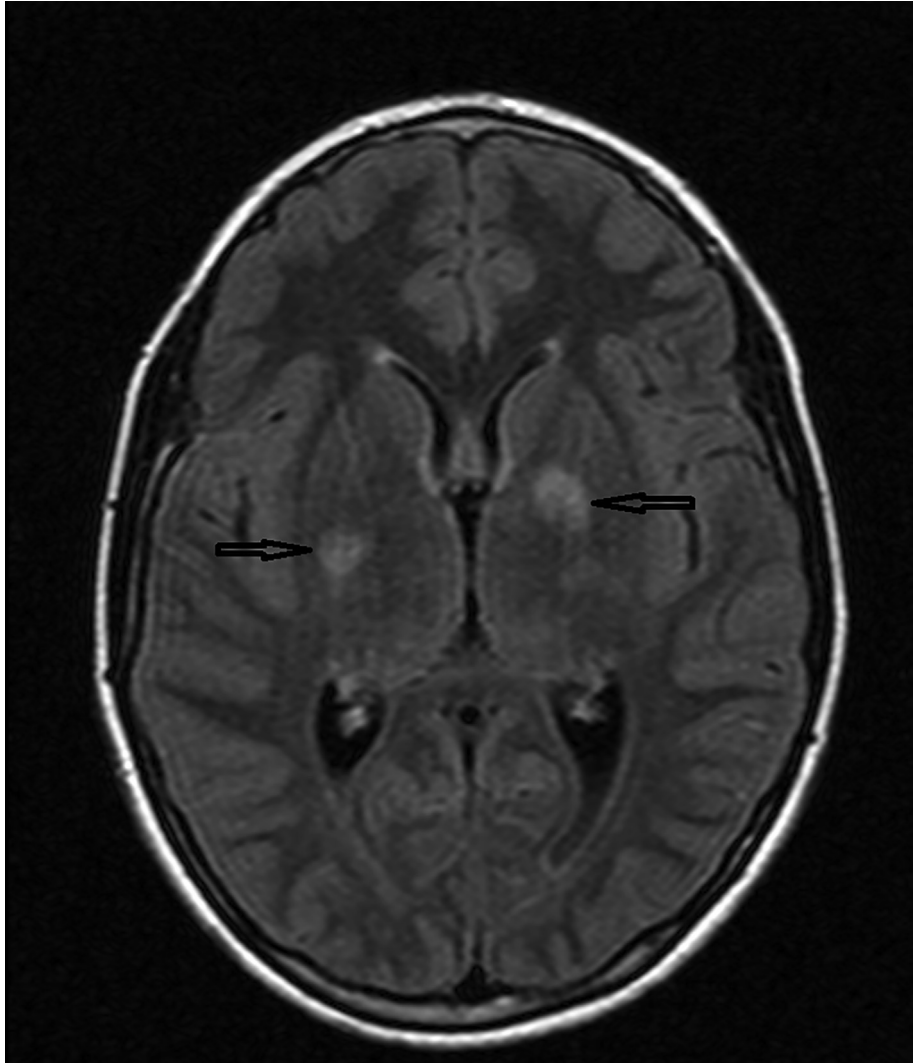
Fig. 3A. FLAIR in axial plane, 11 yr. Boy with NF1, FASI involve basal ganglia (black arrows).

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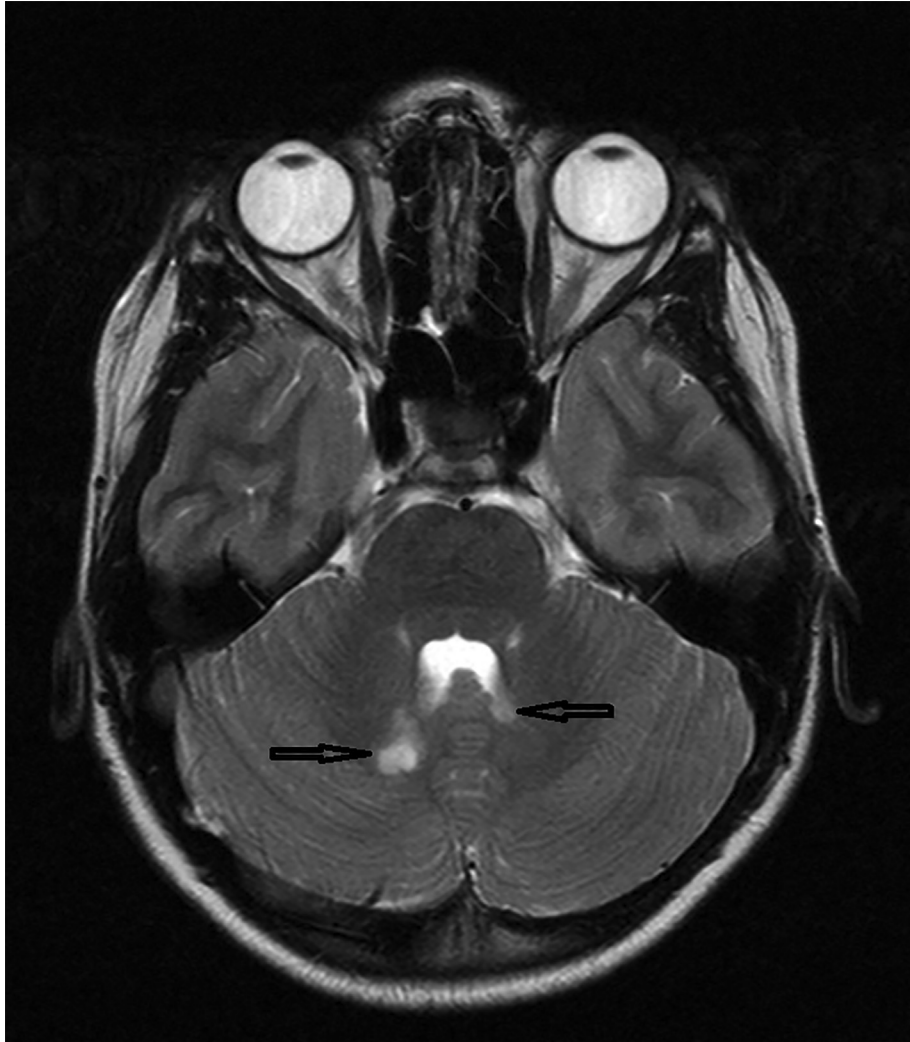
Fig. 3B. T2/TSE in axial plane, FASI involve periventicularly both cerebellar hemispheres (black arrows).

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 inconspicuous 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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The Importance of Advanced Parental Age in the Origin of Neurofibromatosis Type 1

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Von Recklinghausen neurofibromatosis (NF1) is an autosomal dominant disorder with a prevalence about 1/3,000 (1/2,000–1/5,000 in various population-based studies). About 30–50% of cases are sporadic, resulting from a new mutation. NF1 is fully penetrant by mid-childhood, stigmata, and medical problems (neurological, dermatological, endocrine, ophthalmological, oncological) are highly variable. Advanced paternal age (APA) has been known to increase the risk of new germline mutations that contribute to the presence of a variety of genetic diseases in the human population. The trend in developed countries has been toward higher parental age due to various reasons. In a cross-sectional study, in two university hospital centers, data on parental age of 103 children (41 female) born between 1976 and 2005 with sporadic NF1 were analyzed. Parental age at birth was compared with the Czech general population matched to birth year. The mean NF1 sporadic case paternal age at birth was 32.0 years (95% CI 30.7–33.3 years) compared with 28.8 years (95% CI 28.6–29.1 years) in the general population ($P < 0.001$). The mean maternal age at birth was 27.4 years (95% CI 26.3–28.5 years) compared with 25.8 years (95% CI 25.5–26.0 years) in the general population ($P < 0.05$). The case-control difference in the father's age was higher than it was for the mother's age. Sporadic NF1 cases accounted for 35.6% of our entire NF1 cohort. We confirmed an association of advanced parental and particularly paternal age with the occurrence of sporadic NF1.
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Am J Med Genet Part A 158A:519–523.

INTRODUCTION

Von Recklinghausen neurofibromatosis or neurofibromatosis type 1 (NF1), is an autosomal dominant disorder with a prevalence of about 1/3,000 (1/2,000–1/5,000 in various population-based studies) [Rasmussen and Friedman, 2000].

NF1 is highly variable [Friedman, 1999; Goldstein and Gutmann, 2004; Williams et al., 2009]. Typical manifestations are café-au lait skin spots, freckling, peripheral nerve sheath tumors (benign: Neurofibromas; malignant: Neurofibrosarcomas) and other malig-

nancies (intracranial astrocytomas, gastrointestinal stromal tumors, pheochromocytomas, and juvenile monocytic leukemia) [Ferner et al., 2007; Theos and Korf, 2006]. Endocrine symptoms (abnormal thyroid functioning, growth hormone deficiency, and pubertal disorders) are relatively frequent. Neurological and ophthalmological problems may manifest depending on localization of tumors [Ferner et al., 2007].

NF1 is caused by mutations within or deletion of the NF1 gene at 17q11.2. The NF1 gene encodes the protein neurofibromin, which is a negative regulator of the Ras oncogene [Rasmussen and Friedman, 2000].

About 30–50% cases are sporadic and assumed to result from a new mutation [Table I]. There are families documented with more than one sporadic case, each having a distinct NF1 mutation [Klose et al., 1999; Upadhyaya et al., 2003]. Obviously, nonpaternity should also be considered in such cases. In addition, parental mosaicism for an NF1 mutation involving the germline may occasionally account for an ''apparently'' sporadic case [Detjen et al., 2007; Kaplan et al., 2010]. About 80% of intragenic NF1 mutations are paternal in origin, and only about 20% of whole gene deletions are paternal in origin [Lazaro et al., 1996; Upadhyaya et al., 1998]. This may be an important confounder given that about 4% of NF1 cases may be due to a whole gene deletion [Kluwe et al., 2004].

Advanced parental age increases the risk to develop genetic diseases. Over the last two decades, the trend in developed countries has been toward higher parental age due to various factors (family finances, parental education, divorce rates, and reproductive disorders).

An age of a father at the time of conception of ≥40 years and that of mother >35 years is considered as advanced parental age, [Friedman, 1981; de la Rochebrochard and Thonneau, 2003; Toriello and Meck, 2008]. Advanced paternal age (APA) increases the risk of new germline mutations. The male germ line is expected to accumulate point mutations due to replication errors and

reduced activity of repair enzymes, strand mispairing of short tandem repeats, and longer exposure to environmental mutagens [Thomas, 1996; Crow, 2000]. In addition, in human sperm DNA is more methylated than oocyte DNA, which may account for the greater number of paternally derived point mutations occurring within a CpG dinucleotide [Driscoll and Migeon, 1990; Glaser and Jabs, 2004]. APA has been associated with increased fetal death [Nybo Andersen et al., 2004], and with infertility [de la Rochebrochard and Thonneau, 2003], as evident in achondroplasia [Toriello and Meck, 2008], the Apert, Crouzon, and Pfeiffer syndromes [Glaser and Jabs, 2004], bipolar disorders [Frans et al., 2008], schizophrenia [Byrne et al., 2003], and autism [Reichenberg et al., 2006]. Risch et al. [1987] and lately Glaser and Jabs [2004] distinguished mutations in disorders with a strong APA effect from mutations weakly associated with APA, the latter including NF1.

Because of more cell divisions over a prolonged period during spermatogenesis compared to oogenesis the mutation rate for single-locus mutations is higher in men than in women and increases with paternal age [Crow, 1997]. Friedman [1981] calculated the risk for de novo autosomal dominant mutations to be 0.3–0.5% among the offspring of fathers aged >40 years.

Studies on effects of APA in sporadic NF1 have been either inconclusive [Huson et al., 1989; Samuelsson and Akesson, 1989; Takano et al., 1992; Bunin et al., 1997], or have confirmed an APA effect for sporadic NF1 [Sergeyev, 1975; Riccardi et al., 1984; Poyhonen et al., 2000]. We assessed the advanced parental age effect and especially APA effect on the incidence of sporadic NF1 in three decades in the Czech Republic.

MATERIALS AND METHODS

In a cross-sectional study, we assessed parental age in 103 children (41 females) with sporadic NF1 born between 1976 and 2005. Only

TABLE I. Frequency of the Sporadic Cases of Neurofibromatosis Type 1

Author (year)	NF1 patients (n)	Age of patients at the time of evaluation (years)	Sporadic NF1 cases (n)	Sporadic case frequency
Sergeyev [1975]	58[a]	3–70	46[a]	46/58 (79.3%)
Riccardi et al. [1984]	421	X	187	187/421 (44.4%)[b]
Samuelsson and Akesson [1989]	57	X	29	29/57 (50.9%)[b]
Huson et al. [1989]	135	X	41[c]	41/135 (30.4%)[b,c]
Clementi et al. [1990]	110[b]	0.2–40	54[b]	54/110 (49.1%)[b]
Takano et al. [1992]	26	4–36[b]	13	13/26 (50.0%)
Rodenhiser et al. [1993]	58	X	24	24/58 (41.4%)
North [1993]	144	0–68	66	66/144 (45.8%)
McGaughran et al. [1999]	459	0–74	132	132/459 (28.8%)
Poyhonen et al. [2000]	197	0.2–60	77[b]	77/197 (39.1%)[b]
Present study Snajderova et al. [2011]	275[d]	≤ 18	98[d]	98/275 (35.6%)[d]

[a]complete investigation.
[b]calculated from data presented in reference.
[c]direct method, X: Not evaluated.
[d]included data of 98 children from Department of Child Neurology, University Hospital Motol, Prague.

patients with sporadic NF1 younger than 18 years at the time of first examination, who fulfilled NIH criteria for NF1 [NIH Consensus Development Conference, 1988], were enrolled. For all patients the family history was negative. Parents and siblings were examined by NF1 specialists (neurologist, geneticist, endocrinologist, ophthalmologist, and/or dermatologist) and showed no signs of NF1.

All children were Caucasians and born in the Czech Republic. Most were seen in the Clinic for Children with Neurocutaneous Disorders in Prague which provides care to the majority of NF1 children since 1990. Data on maternal and paternal ages were compared with the general age of parents in the Czech population matched to year of birth of each NF1 child (Registry of the National Institute of Healthcare Information and Statistics). Molecular analysis was performed in 20 of the 103 patients [Bendova et al., 2007].

Statistical Analysis

Data are expressed as mean ± SD, $P < 0.05$ was considered to be significant. Means and their 95% confidence intervals were used for description of age and a one-sample t-test was used for testing the null hypothesis. Hotelling's t-test was used for simultaneous testing of equality between groups. A χ^2 goodness of fit test was used for comparison of empirical distribution of the appearance of NF1 in time course to the theoretical uniform distribution.

RESULTS

The proportion of sporadic cases among the NF1 group was 35.6% (98/275). Whereas the paternal age in the Czech population increased significantly since 1990 ($P < 0.001$), such a trend was not observed in fathers (Fig. 1) and mothers (Fig. 2) of NF1 sporadic cases. The mean paternal age at birth of NF1 sporadic cases was 32.0 years (range 19.2–48.3 years; 95% confidence interval (CI) 30.7–33.3 years), while in the general population (matched to birth years) the mean paternal age was 28.8 years (95% CI 28.6–29.1 years) ($P < 0.001$). Fourteen out of 103 fathers (13.6%) were ≥40 years old (Fig. 3).
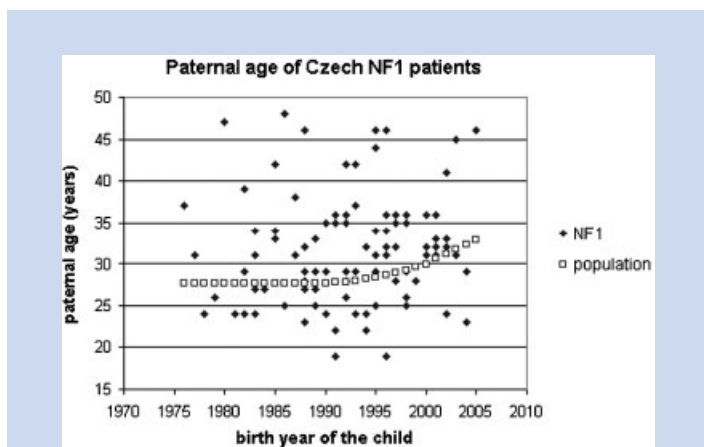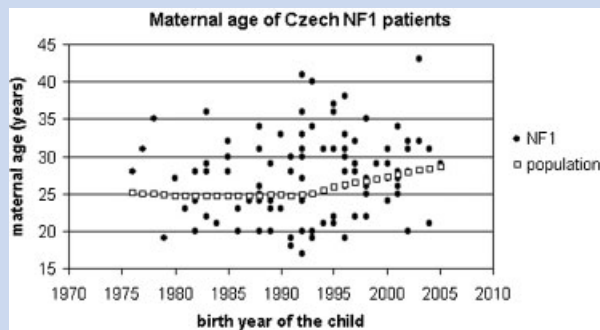
FIG. 2. Maternal age of Czech patients with sporadic neurofibromatosis type 1 compared to the general population.

Mean maternal age at time of birth was 27.4 years (range 17.3–43.1; 95% CI 26.3–28.5 years). In the general population (matched to birth years) the mean maternal age was 25.8 years (95% CI 25.5–26.0 years). Eight out of 103 mothers (7.8%) were ≥35 years old (Fig. 3). In four out of 103 sets of parents (3.9%), the maternal age at birth was >35 years while the paternal age was >40 years.

Simultaneous testing of parents' ages (maternal and paternal) for NF1 and the general population using Hotelling's t-test rejects the null hypotheses of equivalence on the significance level ($P < 0.001$).

DISCUSSION

The frequency of sporadic NF1 cases in our group was 35.6%. In literature the frequency varies from 30% to 50% (Table I). Familial

FIG. 1. Paternal age of Czech patients with sporadic neurofibromatosis type 1 compared to the general population.
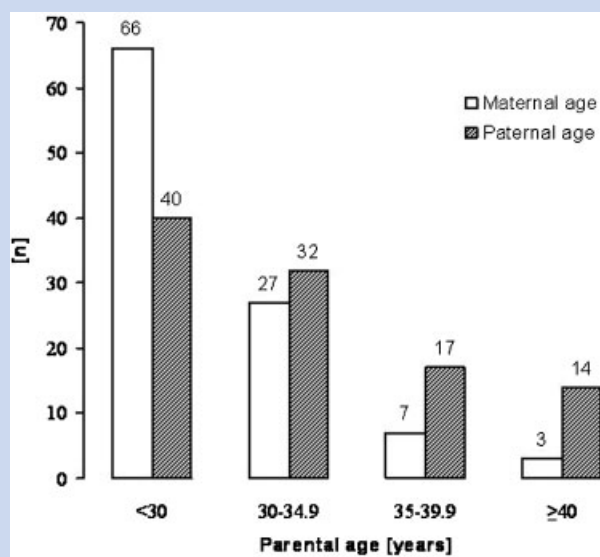
FIG. 3. Age distribution of parents among 103 children with sporadic neurofibromatosis type 1

TABLE II. Parental Age in Previous Studies on Children With Sporadic Neurofibromatosis Type 1

Author (year)	Sporadic NF1 cases (n)	Structure of NF1 group	Controls (method)	Mean paternal age (years)	Paternal age difference (years)	Statistics (P value)	Mean maternal age (years)	Maternal age difference (years)	Statistics (P value)
Sergeyev [1975]	46	CH + A	pop	29.8	2.0	0.03	29.9	1.5	0.08
Riccardi et al. [1984]	187	X	pop	32.8	3.2	<0.001	27.4	1.4	<0.001
Samuelsson and Akesson [1989]	29[a]	CH + A	pop	37.1	3.5	ns	31.7	0.2[a]	ns
Huson et al. [1989]	21[b]	X	pop	29.6	−0.3	0.8	27.7	0.1	0.95
Jadayel et al. [1990]	14	CH + A	pop	29.8	−0.2	ns	X	X	X
Takano et al. [1992]	13	CH + A	pop	35.4	4.5[a]	0.08	30.9	4.0	0.40
Bunin et al. [1997]	89	CH	case-control	29.9	1.5	0.07	26.6	0.9	0.20
Poyhonen et al. [2000]	77[a]	CH + A	pop	33.0	3.0	0.008	30.0	2.5	0.006
Present study Snajderova et al. [2011]	103	CH	pop	32.0	3.2	<0.001	27.4	1.7	<0.05

pop: General population data, ns: Not significant, X: Not evaluated, CH: Children, A: Adults
[a]calculated from data presented in reference.
[b]only in 21 of 41 new NF1 mutations data were available and used in analysis.

cases may be more common than expected because mildly affected family members might have been overlooked without a systematic and experienced clinical examination [Poyhonen et al., 2000].

We analyzed the influence of parental age on incidence of the NF1 in the period 1976–2005. During the last two decades an increasing parental age in the Czech population was observed. Whereas the paternal and maternal age in the general Czech population has been significantly increasing since 1990, an overall similar trend was not apparent in fathers (Fig. 1) and mothers (Fig. 2) of sporadic NF1 children. The number of sporadic NF1 cases born during 1976–1985 compared to the number of those born in 1986–2005 is consistent with an increased incidence. It is also possible that in the earlier period mildly affected patients may have been missed.

The mean age of mothers of sporadic NF1 patients was higher than in the general population (difference 1.7 years; $P < 0.05$), as reported previously [Riccardi et al., 1984; Poyhonen et al., 2000]. The paternal age case-control difference was 3.2 years ($P < 0.001$). The majority of other authors present age difference of 1.5–4.5 years (Table II). Still, only 13.6% of fathers and 7.8% of mothers in our cohort fulfilled criteria of advanced parental age.

Risch et al. [1987] and Glaser and Jabs [2004] distinguished disorders with a strong and weak APA effect: In disorders with a strong APA effect, the fathers of affected children were 5–7 years older compared to the general population, in the disorders with a weak association the fathers were 2–5 years older. In the present study the paternal age difference was 3.2 years. Our results confirm the advanced parental age effect in sporadic NF1, particularly of paternal age.

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Idiopatická stenóza akveduktu a porucha vývoje řeči u dětí s neurofibromatosis von Recklinghausen typ 1 – dvě kazuistiky

Idiopathic Aqueductal Stenosis and Developmental Speech Disorder in Children with Neurofibromatosis von Recklinghausen type 1 – Two Case Reports

Souhrn

Neurofibromatosis von Recklinghausen typ 1 (NF1) je autozomálně dominantně dědičné onemocnění z okruhu neurokutánních syndromů, s incidencí 1 : 2 500–3 000 a vysokým výskytem nových mutací. Jedná se o onemocnění s multisystémovým postižením organizmu s častým výskytem nádorů. Hydrocefalus se u těchto pacientů vyskytuje buď sekundárně při expanzivním procesu mozku, nebo při idiopatické stenóze akveduktu. U dětí jsou velmi často přítomny vývojové poruchy učení, chování a poruchy vývoje řeči. Předkládáme kazuistiku dvou dětí s NF1 se současným výskytem těžké poruchy vývoje řeči a hydrocefalu při idiopatické stenóze akveduktu. U jednoho z dětí došlo k rozvoji stenózy během sledování. Současný výskyt těžké poruchy řeči a hydrocefalu při idiopatické stenóze akveduktu nebyl zatím popsán.

Abstract

Neurofibromatosis von Recklinghausen type 1 (NF1) is an autosomal dominant neurocutaneous disorder, with incidence of 1 : 2,500–3,000 and a high rate of new mutations. This multisystem disorder is frequently associated with tumours. Hydrocephalus in NF1 patients is either secondary to brain expansion or as a result of idiopathic aqueductal stenosis. Learning disability, behavioural problems and speech development disorders are common in NF1 children. We are presenting two case reports of NF1 children with developmental speech disorder and hydrocephalus consequent to idiopathic aqueductal stenosis. One child developed stenosis during follow up. Coincidence of hydrocephalus due to idiopathic aqueductal stenosis and severe developmental speech disorder has not been described yet.

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Úvod

Neurofibromatosis von Recklinghausen typ 1 (NF1) je autozomálně dominantně dědičné neurokutánní onemocnění, s incidencí 1 : 2 500–3 000 a vysokým výskytem nových mutací – 30 až 50 % [1–4]. Diagnóza NF1 je definována na základě sedmi diagnostických kritérií:

1. šest a více skvrn café au lait na kůži,
2. freckling v inguinální nebo axilární oblasti,
3. dva neurofibromy a/nebo jeden plexiformní neurofibrom,
4. Lischovy noduly,
5. gliom optiku,
6. kostní změny,
7. příbuzný prvního stupně.

Ke stanovení diagnózy je potřeba nalézt alespoň dvě z těchto diagnostických kritérií [5]. Gen NF1 se nachází na dlouhém raménku chromozomu 17 v oblasti 11.2 (17q11.2), patří mezi tumor-supresorové geny a jeho genový produkt neurofibromin se podílí na regulaci Ras-MAPK signální dráhy [4]. NF1 je onemocnění s multisystémovým postižením organizmu a častým výskytem nádorů zejména centrálního i periferního nervového systému.

Nejčastějšími patologickými nálezy na MR mozku jsou gliomy optiků, gliomy lokalizované mimo zrakovou dráhu a hypersignální ložiska v T2 vážených obrazech na MR mozku (FASI, Foci of Altered Signal Intensity, nazývané také UBOs – Unidentified Bright Objects či hamartomy). Dle současných znalostí jsou FASI ložiska způsobená aberatní myelinizací, nemají nádorový charakter a nejsou příčinou ložiskové symptomatiky [4,6,7].

Hydrocefalus se u NF1 pacientů objevuje buď sekundárně při expanzivním procesu mozku (nádor, arachnoidální cysta atd.), nebo při idiopatické stenóze distální části akveduktu [1,2,7,8].

Kognitivní deficity patří mezi nejčastější komplikace NF1. Vývojové poruchy učení a/nebo chování se vyskytují u 50–60 % dětí s NF1 [9]. Neverbální a verbální poruchy vývoje řeči jsou popisovány u 30–60 % dětí s NF1, rozšířeny jsou poruchy jemné i hrubé motoriky [4].

Pacient 1

Chlapec je z neúplné rodiny (otec neznámý), matka bez známek NF1. Dítě
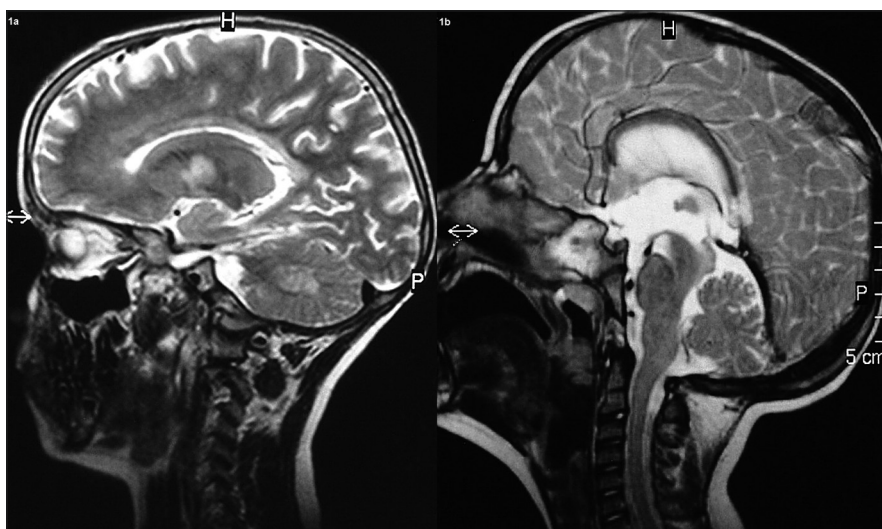
Obr. 1a, b) T2 turbo spin echo sekvence v sagitální rovině – bez hydrocefalu, patrná ložiska FASI v bazálních gangliích a mozečkové hemisféře (a), supratentoriální hydrocefalus, se zúžením terminální části dilatovaného mokovodu (b).

z 1. fyziologické gravidity, porod ve 42. týdnu, indukovaný, porodní hmotnost, délka a poporodní adaptace byly v normě, pro ikterus měl krátce fototerapii. Skvrny café au lait byly patrné asi od jednoho roku věku, psychomotorický vývoj byl od počátku nerovnoměrný a od batolecího věku byly pozorovány poruchy spánku. Ve třech letech se objevil první epileptický záchvat s adverzí hlavy a očí doprava, hypersalivací, poruchou vědomí a následným zvracením. V místě bydliště byl nasazen fenytoin a ten byl pro neúplnou kompenzaci záchvatů vyměněn za karbamazepin.

Ve věku pěti let byl pro mentální retardaci a epilepsii doporučen k první hospitalizaci na KDN FN Motol. V objektivním neurologickém nálezu byl výrazný psychomotorický neklid, mentální retardace, porucha vývoje řeči (rozumí, odpovídá jednotlivými slovy, s latencí), konvergentní strabizmus vlevo, hyperreflexie na pravostranných končetinách a skolióza. Na kůži byly nalezeny skvrny café au lait (v diagnostickém počtu a velikosti pro NF1), nevýrazný inguinální freckling a dva neurofibromy. Již dle kožního nálezu byla stanovena diagnóza NF1. Vyšetření očního pozadí bylo bez městnání, přední segment s nálezem Lischových nodulů. Na MR mozku byl popsaný gliom prechiazmatické části levého optiku, suspektní gliom pravého optiku a vícečetné FASI v typických lokalizacích. Komorový systém byl při tomto prvním MR mozku

štíhlý (obr. 1a). MR míchy bylo v normě, bez nálezu paravertebrálních neurofibromů či durálních ektázií. Vyšetření evokovaných potenciálů bylo s normálním nálezem latencí při vyšetření VEP i BAEP, ale amplituda odpovědi VEP byla velmi vysoká (až 50 uV). EEG bylo v širších mezích normy – jen s lehce abnormální základní aktivitou a epizodami rytmických pomalých vln s pravostrannou převahou. Dle ORL sluch v normě, psycholog hodnotil PMV jako nerovnoměrný, opožděný do pásma středně těžké mentální retardace, s nejrozvinutější složkou hrubé motoriky, řeč jako vývojovou dysfázii s podílem mentální retardace a neadekvátní stimulace.

V sedmi letech věku se změnil charakter epileptických záchvatů – v úvodu bolest hlavy, zvracení, porucha kontaktu, hypotonie, bez křečí, poté spavost, v neurologickém nálezu byla nově popsána (při porovnání s první hospitalizací) bilaterální lehká paréza n. VI více vlevo a pyramidová iritace na levostranných končetinách. Přetrvávala porucha vývoje řeči, mentální retardace a skolióza. Chlapec byl bez dalších příznaků nitrolební hypertenze. Na kontrolním MR mozku byl nález dekompenzovaného supratentoriálního hydrocefalu na podkladě stenózy distální části akveduktu, bez ložiskových změn v okolí stenózy (obr. 1b). Ložiska FASI byla v typické lokalizaci a také gliomy obou optiků byly stacionární. Při akutní neurochirurgické operaci byl zaveden VP zkrat, vývoj
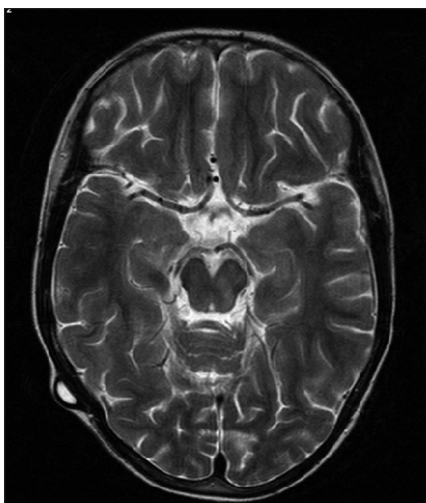
Obr. 2. T2 turbo spin echo sekvence v transverzální rovině – ložiska FASI v mezencefalu a parahipokampálně, chybí výpadek signálu z proudění v lumen mokovodu.

řeči mírně postupoval, stran epilepsie byl kompenzovaný, bez nutnosti úpravy medikace. Následně s odstupem devíti měsíců došlo k akutnímu zhoršení neurologického nálezu včetně zhoršení poruchy řeči. Na MR mozku byla dekompenzace supratentoriálního hydrocefalu, ostatní nálezy byly stacionární.

Od neurochirurgické revize VP zkratu jsou opakované kontrolní MR mozku se stacionárním nálezem (obr. 2), ložiskový neurologický nález je dlouhodobě beze změny, epileptické záchvaty se objevují sporadicky. Stále však dochází k pomalému zhoršování z hlediska mentálního – při kontrolním psychologickém vyšetření ve věku 12 let byl patrný regres, rozu-

mové schopnosti hodnoceny v pásmu středně těžké mentální retardace s nejvýraznějším postižením mnestických funkcí, vývojová dysfázie a dysartrie s dalším zhoršením kvality řeči. Chlapec je i nadále v našem sledování.

Byla provedena přímá DNA analýza genu NF1 s nálezem kauzální mutace v exonu 4c. Mutace typu missense c.647 T > C způsobuje záměnu aminokyselinových zbytků v řetězci genomové DNA, p.Leu216Pro, a je pravděpodobnou příčinnou vzniku nefunkčního genového produktu. Mutace byla prvně popsána Fasholdem et al [10], nikoliv však v souvislosti s podobným fenotypem pacienta.

Pacient 2

Dívka z 1. fyziologické gravidity, porod v termínu, bez komplikací, porodní váha, délka i poporodní adaptace byly v normě. Rodinná anamnéza je nevýznamná, bez příznaků NF1. Skvrny café au lait byly patrné od narození, psychomotorický vývoj byl až do tří let věku v normě, včetně vývoje řeči. Od čtyř let zhoršování kvality řeči, nejprve balbuties, postupně až rozvoj fatické poruchy se složkami expresivní afázie. Dívka měla opakovaně vyšetření sluchu s normálním nálezem.

První hospitalizace na KDN FN Motol proběhla v osmi letech věku pro poruchu vývoje řeči a bolesti hlavy. V neurologickém nálezu byla makrocefalie, centrální paréza n. VII vpravo, lehká pravostranná zániková hemiparéza, výrazná neobratnost a porucha řeči. Na kůži byly nalezeny skvrny café au lait (v diagnostickém počtu a velikosti pro NF1), dále počínající axilární freckling a plexiformní neurofibrom

na pravém předloktí. Již dle kožního nálezu byla stanovena diagnóza NF1. Oční pozadí bylo už při přijetí s nálezem městnání vpravo a incipientním městnáním vlevo. Na prvním MR mozku byl nález supratentoriálního hydrocefalu s naznačeným transependymálním pronikáním likvoru, s nápadným zúžením terminální části dilatovaného mokovodu, bez ložiskových změn v okolí stenózy (obr. 3a). Na MR byly také popsány FASI supra- i infratentoriálně a rozšíření obalů optických nervů oboustranně, bez znamek gliomů optiku či chiazmatu. Stav byl řešen zavedením interventrikulostomie. Dále byla dívka ve stabilizovaném stavu, přechodně došlo i ke zlepšení řeči.

V 10 letech věku nastalo opět zhoršení kvality řeči a zvýraznění únavnosti. Dále se začaly objevovat stavy s bolestí hlavy, nauzeou a zvracením, často s vegetativním doprovodem v obličeji (zarudnutí, pocení), které ustupovaly po vyspání. V aktuálním neurologickém nálezu byla makrocefalie, blokáda C páteře, porucha statiky a dynamiky Th-L páteře, skolióza, pyramidová iritace na dolních končetinách více vpravo a porucha řeči. Oční pozadí bylo bez městnání, kontrolní MR mozku bez znamek dekompenzace hydrocefalu, bez nálezu expanzivního procesu (obr. 3b). EEG bylo lehce abnormální pro známky ospalosti a příměs pomalých vln bitemporálně s převahou vlevo, s negativní fotostimulací. Psycholog hodnotil dívku v pásmu lehké mentální retardace. Obtíže jsme uzavřeli jako migrenózní bolesti hlavy s podílem vertebrogenním.

Během dalšího sledování (do 19 let věku) nedošlo k dekompenzaci hydrocefalu ani ke vzniku nádoru mozku. I přes intenzivní logopedickou péči se kvalita řeči nezlepšila. Během dispenzarizace byla zjištěna hraniční hypertenze, byl vyloučen feochomocytom i cévní změny renálních arterií, medikace prozatím nebyla nasazena. Elektrofyziologická vyšetření (evokované potenciály – VEP, BAEP) byly opakovaně v normě.

Mutační analýza genu NF1 odhalila v exonu 29 pravděpodobně kauzální mutaci typu delece, c.5220delT. Mutace vede k posunu čtecího rámce s následným vznikem terminačního kodonu, c.Ser1741Valfs3X. Předčasné ukončení translace proteinu vede k vytvoření zkráceného genového produktu, jehož funkce je tím omezena. Mutace
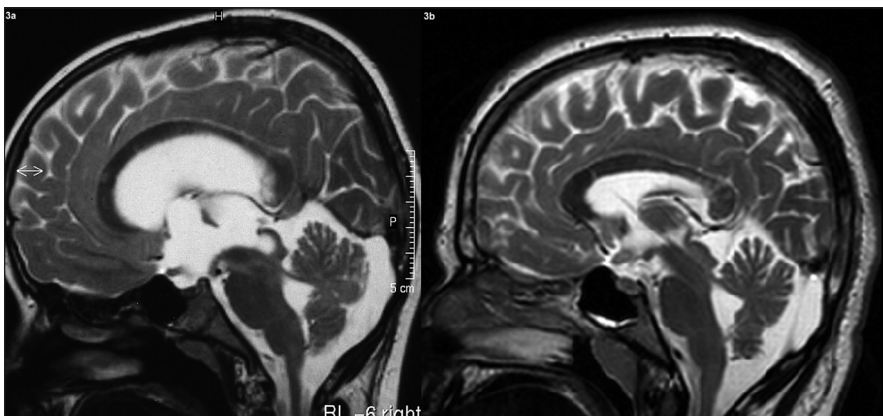
Obr. 3a, b) T2 turbo spin echo sekvence v sagitální rovině – supratentoriální hydrocefalus se stenózou mokovodu (a) regrese hydrocefalu po zavedení zkratu z postranní komory přes III. komoru a mokovod do IV. komory (b).

byla prvně popsána v souvislosti s naším pacientem [11].

Diskuze

První zmínky o hydrocefalu na podkladě stenózy akveduktu jsou již z roku 1927 a 1940 [7,8]. Frekvence výskytu idiopatické stenózy akveduktu u pacientů s NF1 je 1,2–2 % a ve většině případů je zjištěna během první, případně druhé dekády života [1,2,7,9,12]. U našich pacientů byla stenóza distální části akveduktu s rozvojem hydrocefalu nalezena v první dekádě života. U pacienta 1 došlo k rozvoji stenózy akveduktu a následného hydrocefalu v průběhu našeho sledování. Podobné pozorování jsme v literatuře nenalezli.

Hydrocefalus se u pacientů s NF1 vyskytuje v 1–4 % [1,7]. Créange et al [1] popisují hydrocefalus u 7/158 (4 %) NF1 pacientů (138 dospělých, 20 dětí), přičemž u dětí byl výskyt hydrocefalu častější (6/20) než v dospělosti (1/138). Hydrocefalus při stenóze akveduktu popisují Créange et al [1] u čtyř dětí ze sledované skupiny, z toho u jednoho pacienta byl hydrocefalus asymptomatický – bez příznaků nitrolební hypertenze. U obou prezentovaných pacientů byl syndrom nitrolební hypertenze neúplně vyjádřen a rozvoj hydrocefalu dlouhodobě unikal pozornosti. Předpokládáme, že se na tom podílela pomalá progrese stenózy distální části akveduktu, s pozvolným nárůstem nitrolebního tlaku. Žádný z autorů neuvádí jako komplikaci rozvoje hydrocefalu u pacientů s NF1 poruchu vývoje řeči nebo její regres. Obecně lze regres kvality řeči při dekompenzovaném hydrocefalu v některých případech očekávat. U prvního z našich pacientů byla porucha vývoje řeči patrná od počátku, tedy prokazatelně před rozvojem hydrocefalu. U druhé pacientky došlo ke zhoršení řeči ve čtyřech letech – předpokládáme, že

také před rozvojem hydrocefalu, i když z tohoto období nemáme k dispozici zobrazení CNS, ale usuzujeme tak vzhledem k dlouhému, čtyřletému období bez dalších obtíží, které předcházelo manifestaci dekompenzovaného hydrocefalu. Po úspěšném operačním řešení hydrocefalu u prvního pacienta nedošlo ke zlepšení řeči, u druhé pacientky jen k přechodnému mírnému zlepšení a během dalšího sledování kvalita řeči kolísala. A proto zvažujeme možnou souvislost poruchy řeči s rozvojem stenózy distální části mokovodu. Přes značnou podobnost klinického obrazu jsou nalezené mutace NF1 genu odlišné.

Leisti [7] uvádí hypotézu o přímé expresi NF1 genu v oblasti distální části akveduktu. Většina autorů [1–4,9,12] se k příčině stenózy nevyjadřuje a výše uvedenou hypotézu neuvádí. Příčinu rozvoje stenózy distální části akveduktu u NF1 tedy považujeme za dosud neobjasněnou.

Námi nalezené kauzální mutace jsou rozdílné povahy i lokalizace, nenacházejí se v žádné z doposud funkčně objasněných domén neurofibrominu. Jejich přesné působení na rozvoj onemocnění není známo.

Závěr

Hydrocefalus představuje závažnou až život ohrožující komplikaci diagnózy NF1 a s výskytem této komplikace je nutné počítat. Současný výskyt a/nebo vztah poruchy vývoje řeči a hydrocefalu při idiopatické stenóze akveduktu nebyl v literatuře dosud popsán. Na předkládaných kazuistikách dokládáme, že těžká porucha vývoje řeči může být jedním ze signálů pomalu se rozvíjející stenózy distální části akveduktu, která postupně vede k hydrocefalu. Těžká porucha vývoje řeči by měla být jednou z indikací k provedení zobrazení mozku u pacienta s NF1, nejlépe MR mozku včetně MR PC (Phase Contrast)

v cine modu, což je vyšetření umožňující zobrazit průtok moku akveduktem.

Použité zkratky

NF1	NeuroFibromatosis von Recklinghausen typ 1
FASI	Foci of Altered Signal Intensity
KDN FN Motol	Klinika dětské neurologie 2. LF UK a FN v Motole, Praha
n	nerv

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