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 Listerick 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 nursing evaluation of psychomotor development, annually during follow up, at least once, and in patients with neurologic symptoms/problems as frequently as needed. Ophthalmological 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, sagittal 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 x 10 mm (height x 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 andLM+/−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 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 (fulfit 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.

Neurosurgery 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 suspicion 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 – huge OPG or progression with ophthamologic problems as decrease or worsening 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. Forty-one/16 had normal visus, 2/16 had amblyopia and visual impairment, all patients were not treated. Forteen/16 had normal visus, 2/16 had endocrinologic problems. Sixteen/42 Dodge 2 OPG were from Dodge 2 + H subgroup.

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 treated 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

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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.
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.
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
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 \times width) \text{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 \pm 0.04 mm, just posterior to the globe, decreasing to 3.50 \pm 0.04 mm posteriorly), and Votruba et al. (3.5 \pm 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 endocrinological. Moreover, these tumours could also cause hydrocephalus. The treatment indica-
tion criteria assess not only clinical and imaging findings, but also quickness 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]. Lister-nick 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...
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% of 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. 3A. FLAIR in axial plane, 11 yr. Boy with NF1, FASI involve basal ganglia (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.

Fig. 3B. T2/TSE in axial plane, FASI involve periventricularly both cerebellar hemispheres (black arrows).
Table 4
Patients with idiopathic aqueduct stenosis and clinical signs of hydrocephalus.

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

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 [Friedman, 1999; Goldstein and Gutmann, 2004; Williams et al., 2009].

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-

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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 germine 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 [Lazar 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 [Bryne 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
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 \( \chi^2 \) 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).

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
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 increasing parental age in the Czech population was observed. The majority of other authors present age difference of 1.5–7 years older compared to the general population, in the 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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REFERENCES


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 neurocutánních syndromů, s incidencí 1 : 2 500–3 000 a vysokým výskytovou nových mutací. Jedná se o onemocnění s multisystémovým postižením organismu s častým výskytom 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 výskytom 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.
Úvod
Neurofibromatosis von Recklinghausen typ 1 (NF1) je autozomálně domi-
nantně dědičné neurocutánní onemocnění, s incidencí 1 : 2 500–3 000 a vy-
sokým výskytom nových mutací – 30 až 50 % [1–4]. Diagnostika NF1 je defino-
vána 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 plexi-
formní neurofibrom,
4. Lischovy noduly,
5. gliom optiku,
6. kostní změny,
7. příbuzný prvního stupně.

Ke stanovení diagnózy je potřeba nalézt alespoň dvě z těchto diagnostick-
kých kritérií [5]. Gen NF1 se nachází na dlouhém raménku chromozomu 17 v ob-
lasti 11.2 (17q11.2), patří mezi tumor-suppresorové geny a jeho genový produkt
neurofibromin se podílí na regulaci Ras-
MAPK signální dráhy [4].
NF1 je onemocnění s multisystémovým
postižením organismu a částým výskytom
nádorů zejména centrálního i v nervového
systému.
Nejčastějšími patologickými nálezy na
MR mozku jsou gliomy optiku, gliomy lo-
kalizované mimo zrakovou dráhu a hyper-
signální ložiska v T2 vážených obrazech
na MR mozku (FASI, Foci of Altered Signal
Intensity, nazývané také UBOs – Uniden-
tified Bright Objects či hamartomy). Dle
současných znalostí jsou FASI ložiska způ-
sobená aberonat myelinizace, nemají ná-
dorový charakter a nejsou příčinou ložis-
kové symptomatické [4,6,7].
Hydrocefalus se u NF1 pacientů ob-
jevuje buď sekundárně při expanzivním
procesu mozku (nádor, arachnoidální
zystycta ad.), nebo při idiopatické stenóze
distální části akveduktu [1,2,7,8].
Kognitivní deficití patří mezi nejčas-
tější komplikace NF1. Vývojové poru-
chy učení a/nebo chování se vyskytují u
50–60 % dětí s NF1 [9]. Neverbalní a
verbální poruchy vyvojové řeči jsou popi-
souvány u 30–60 % dětí s NF1, rozšířeny
jsou poruchy jemné i hrubé motory [4].

Pacient 1
Chiacec je z neúplné rodiny (otec ne-
známa), matka bez známek NF1. Dítě
z 1. fyzioologické gravidity, porod ve
42. týdnu, indukován, porodní hmot-
nost, délka a poporodní adaptace byly v
normě, pro ikterus měl krátké fototo-
rapii. Skvrny café au lait byly patrné asi
od jednoho roku věku, psychomotorický
vývoj byl od počátku nerovnoměrný a
s počátku též častými výskyty skvrn café au
lait (vážené obrazy) [4]. V sedmi letech se objevil první
epileptický záchvat s adverzi hlavy a očí
a doprava, hypersalivacií, porouchou vědomí
a následnými zvracením. V místě bydléšti
byl nasazen fenytolin, porodní hmot-
nost, délka a příčinou ložis-
kové symptomatické [4,6,7].

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lait (vážené obrazy) [4].
Obr. 2. T2 turbo spin echo sekvence v transversální rovině – ložiska FASI v mezencefalu a parahipokampálně, chybí výpadek signálu z proudění v lumen mokovodu.

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).


Dívka měla opakovaně vyšetřovat v nutností užívat nosních čepicí.

V 10 letech věku nastalo opět zhoršování kvality řeči a výraznější na nemoci. Dále se začaly objevovat stavy s bolestí hlavy, nahuťování a zvracením, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větším zvětšením opf. V přijímání byla zjištěna zvracená, často s větší
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 akveduktu a následného hydrocefalu v průběhu našeho sledování. Podobné pozorování jsme v literaturě nenalezli.


Leistí [7] uvádí hypotézu o přímé expresu NF1 genu v oblasti distální části akveduktu. Většina autorů [1–4,9,12] se k příčině stenózy neuvádí jako komplikaci rozvoje hydrocefalu při NF1, nejlépe MR. Neuroradiologické zobrazení CNS, ale usuzujeme tak vzhledem k dlouhému, clyfetému období bez dalších obtíží, které předcházelo manifestaci dekompenzovaného hydrocefalu. Přes značnou podobnost klinického obrazu jsou nalezené mutace NF1 genu odlíšné.

Námi nalezené kauzální mutace jsou rozdílné povahy i lokalizace, nenacházejí se v žádné z dopouštěně funkčně obsazených 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. Současně bylo toto vztah pochází vývoje řeči a hydrocefalu při idiopatické stenóze akveduktu nebylo v literatuře dosud popsáno. Na předkládaných kauzálních těžké porucha vývoje řeči může být jedním ze signálů případu hydrocefalu. Těžká porucha vývoje řeči by měla být jednou z indikací k provedení zobrazení mozku u pacienta s NF1, nejlepší MR mozku včetně MR PC (Phase Contrast) v ciné mode, což je vyšší léčení umožňující zobrazit průtok moku akveduktem.

Použité zdroje

NF1 Neurofibromatosis von Recklinghausen type 1
FASI Foci of Altered Signal Intensity
KDN FN Motol Klinik dětské neurologie 2. LF UK n AN v Motole, Praha nerv

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