Clinical case

**Von Hippel-Lindau disease and aggressive GH-PRL pituitary adenoma in a young boy**

**Maladie de von Hippel Lindau et adénome hypophysaire agressif GH-PRL chez un jeune garçon**

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Available online 20 January 2012

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**Abstract**

Von Hippel-Lindau disease is an autosomal dominant disorder involving the development of specific tumours in multiple organs, both benign and malignant. In the CNS, the syndrome is characterized by haemangioblastomas of the retina, spinal cord and brain. We report the case of a 15-year-old boy with the diagnosis of aggressive GH-PRL pituitary macroadenoma and a family history of VHL disease. Pituitary resection was performed, although complete excision of the lesion could not be confirmed by the neurosurgeon. A control MRI was done 6 months after surgery and the pituitary lesion was similar to the presurgical image. A second operation allowed partial resection of the tumour followed by targeted radiotherapy. Pituitary adenomas are rare benign tumours in children with macroadenomas observed mainly in boys. These tumours in adolescents often occur in a familial setting or in the context of known genetic defects. Angiogenesis is an important feature of pituitary adenomas and a possible inhibitory role of pVHL in pituitary angiogenesis has been suggested. This GH-PRL pituitary macroadenoma with a VHL mutation might be of particular aggressiveness. Pituitary adenomas are not classically described in VHL syndrome and the medical community should be alerted to its rare occurrence in this location.

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**Résumé**

La maladie de von Hippel-Lindau, autosomique dominante, implique le développement de tumeurs spécifiques dans de multiples organes. Dans le SNC, le syndrome est caractérisé par des hémangioblastomes (rétine, moelle épinière, cerveau). Nous rapportons le cas d’un garçon de 15 ans avec un macroadénome hypophysaire agressif GH-PRL et une histoire familiale de maladie de VHL. Une résection hypophysaire a été réalisée, sans exérèse complète de la lésion selon le neurochirurgien. UneIRM de contrôle a été faite six mois aprèst et l'image de la lésion hypophysaire était semblable à l’image préopératoire. Une seconde opération a permis une résection partielle de la tumeur suivie d’une radiothérapie ciblée. Les adénomes hypophysaires sont des tumeurs bénignes rares chez les enfants (macroadénomes plus fréquents chez les garçons). Ces tumeurs surviennent souvent dans un cadre familial ou dans un contexte de maladies génétiques chez les adolescents. L’angiogenèse est une caractéristique importante des adenomes hypophysaires et un rôle inhibiteur possible des pVHL dans l’angiogenèse hypophysaires a été suggéré. Ce macroadénome hypophysaire GH-PRL associé à une mutation VHL pourrait être d’une agressivité particulière. Les adenomes hypophysaires ne sont pas classiquement décrits dans le syndrome de VHL et la communauté médicale doit être alertée de cette rare localisation.

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1. **Introduction**

Von Hippel-Lindau disease (VHL) is a highly penetrant inherited autosomal dominant multisystem disorder characterized by...
abnormal growth of blood vessels resulting in haemangioblastomas and cysts, as well as development of other tumours in several organs. The syndrome is characterized by haemangioblastomas of the retina, spinal cord and brain, renal cysts and clear cell renal carcinoma, phaeochromocytoma, endolymphatic sac tumours, multiple pancreatic cysts, cyst adenomas or neuroendocrine tumours of the pancreas [1].

With the exception of renal clear cell carcinoma, practically all tumours are usually benign but they may have a deleterious effect on tissues in their vicinity, resulting in a range of symptoms and secondary damage, due to their expansive nature.

The incidence of VHL is one in 36,000 live births and it is caused by germline mutations of the VHL tumour-suppressor gene located on chromosome 3p25-26 [2].

In the familial form, one single mutated gene is transmitted to descendants. In the carriers of this predisposition, the second gene (the security gene) in a body cell must undergo a mutation (second hit) to induce cell proliferation.

Pituitary adenomas are rare benign tumours in children although they become more frequent in adolescents [3]. Macroadenomas are more often observed in boys. We report the first case of VHL syndrome associated with pituitary tumour in a young boy.

2. Clinical case

An 18-year-old boy was referred at the age of 15 for decreased visual acuity of the right eye. This was confirmed by ophthalmologic examination showing decreased visual acuity (2.5/10th) and bitemporal quadranopsia. Two retinal vascular lesions had already been diagnosed and photocoagulated.

There were no signs of puberty on clinical examination, his height was 1.46 m (−3.5 SD) and his weight was 37 kg (−5 SD). No renal lesion was found on ultrasound examination.

The family history revealed VHL in his mother, who died at the age of 40, and in his maternal aunt and grandmother, deceased at 30 and 33 years, respectively (Fig. 1). Many haemangioblastomas were observed in the CNS of these people. His mother was operated on three times for cerebellar haemangioblastomas, the first at 13 years of age. She had also been treated for bilateral retinal haemangioblastomas since the age of 19. In addition, she had surgery for a renal tumour at the age of 32 and also had pancreatic cysts. She died of the diffuse haemangioblastomas in the posterior fossa.

On genetic testing, it was found that the patient carried the familial germline mutation located in the first exon of the VHL gene (c.340G > C, p.Gly114Arg). The research of AIP gene mutation was negative.

Cerebral MRI examination (Fig. 2) visualized a voluminous pituitary adenoma with suprasellar extension compressing the optic fibres invading both cavernous sinuses. It also confirmed two small cerebellar haemangioblastomas.

Fasting hormone evaluation at 8 a.m. revealed high PRL, 1658 mIU/l (53–310), normal GH 15.6 mIU/l (0.26–20.3) and IGF1 180 ng/ml (140–690) levels; cortisol 428 nmol/l (N 8 a.m. 305–750) and ACTH 26.6 pmol/l (10–50); testosterone 1.0 nmol/l (7.6–27.7), LH 0.71 IU/l and FSH 2.97 IU/l; TSH 2.1 mIU/l and FT4 26.6 pmol/l (10–24).

A transphenoidal pituitary resection was performed (M.J.), with some doubt about total excision of the adenoma. The pathology examination, including immunocytochemistry and proliferation markers (Fig. 3), made the diagnosis of a sparsely granulated GH-PRL pituitary adenoma (60–80% of PRL and GH immunoreactive cells) with fibrous bodies of cytokeratin and a high proliferation rate (10 mitoses/10 fields × 40), Ki-67 index at 4%, positive p53 staining in rare nuclei. Numerous large vessels were also observed without abnormalities. Because of the absence of clinical and biological signs of acromegaly and the presence of signs of invasion in the cavernous sinus, the anatomical diagnosis was invasive silent GH-PRL adenoma with a high proliferation rate.
Fig. 3. GH-PRL adenoma with 60 to 80% of GH (A) and PRL (B) immunoreactive cells, with numerous mitoses (two in this field) and Ki-67 index at 4% (C). Immunoperoxidase reaction, X100 and X200.

The post-surgical PRL level was still increased (886 mIU/l) and treatment with cabergoline was begun, allowing normalization. During an ITT test, the GH level was only 4.53 mIU/l (N > 20) in spite of a glycaemia level of 1.99 mmol/l, and the IGF1 level was 115 ng/ml (75–500). The family tried to insist upon substitutive GH treatment to correct his short stature but this was refused due to the potentially aggressive pituitary tumour. Six months after surgery, a follow-up MRI revealed that the voluminous image of the macro adenoma was unchanged. Five months later, a new MRI was identical. In view of the clinical improvement and the apparent stability of the image, a “ghost image” was suspected.

Height was 1.50 m (−4 SD) and weight 38 kg (−5 SD) on clinical examination 1 year after surgery, with evidence of onset of puberty, both testicles measuring 40 × 20 mm. Bone age was estimated at 12 years.

Puberty stage P3A1 was recorded at clinical examination two and a half years after surgery, testicles measuring 45 × 25 mm. His height was 1.53 m (−3.6 SD), weight 39.5 kg (−5 SD), and BMI 17 kg/m². Bone age was estimated at 14 years (chronological age 18). PRL was 420 mIU/l (150–330), IGF1 128 ng/ml (75–500), testosterone 10.4 nmol/l (11.3–34.7) and SHBG 226 nmol/l (20–70). Facing low BMI and very high SHBG level, dietary review revealed no food restriction or malabsorption.

MRI performed at this time visualized a tissue process in the pituitary gland. This tissue was invading the cavernous sinus and extended significantly into the suprasellar region with a mass effect on the optic chiasm. The image of persistent adenoma had increased compared to the postoperative MRI. A cystic part of the main haemangioblastoma was also noted in the right cerebellum image (Fig. 4). No abnormal secretion of methoxyamines was detected and renal ultrasound examination was persistently normal.

A second surgical intervention was, therefore, performed (P.F.) by a transfrontal route but the excision was probably incomplete because residual tissue was noted by the neurosurgeon in both cavernous sinuses and along the medial wall of the left cavernous sinus (Fig. 5). Complementary stereotaxic radiotherapy was, therefore, performed. After radiotherapy, a somatostatin analog was added to the cabergoline treatment to try to prevent progression of this aggressive somatolactotrophic adenoma.

At the second pathology examination, the diagnosis was a GH-PRL pituitary adenoma with numerous mitoses (five mitoses/10 fields × 40) but Ki-67 and p53 staining was negative.
Fig. 4. Cerebral MRI 3 years after first operation.

3. Discussion

We present the case of a 15-year-old boy with a familial history of VHL disease expressed mainly by haemangioblastomas. Two retinal lesions, which appear at a much younger age in VHL patients than in sporadic cases [4], had been treated by laser therapy. A pituitary macroadenoma was then discovered due to a decreased visual acuity with bitemporal quadranopsia, growth failure with short stature for age and lack of pubertal development.

The first histopathology examination revealed a GH-PRL adenoma, with a high proliferation rate (Ki-67: 4%; 10 mitoses/10 fields × 40, p53 negative) and, after the second intervention, numerous mitoses (five mitoses/10 fields × 40) were also noted but Ki-67 and p53 staining was negative, suggesting tumour dedifferentiation.

Endocrine glands are typically vascular organs. Angiogenic factors are involved in cell growth, proliferation and migration. Angiogenesis is also regulated by hormonal changes such as increased estrogens or IGF-1 [5]. A relationship between angiogenesis and tumour size, tumour invasiveness, and aggressiveness has been shown in some pituitary tumours, but not in others [5]. VEGF expression, in GH adenomas, has also been described [5]. VHL protein (VHL-P) was studied in seven non-tumour pituitary glands and 68 pituitary adenomas by immunocytochemistry using a polyclonal antibody which detects both normal and mutated forms [6]. In non-tumour pituitary glands, VHL-P was variably expressed in the cytoplasm of most anterior pituitary cells. In densely (eight cases) and sparsely (seven cases) granulated somatotrophic adenomas, nuclear and weak cytoplasmic immunoreactivity was common; all four sparsely granulated lactotrophic adenomas had only moderate cytoplasmic immunostaining. A more recent study showed that vascularisation of microprolactinomas were less pronounced compared to macroprolactinomas but this was not observed for GH-secreting tumours [7]. Assessment of cell proliferation using Ki-67 showed no association between angiogenesis using microvascular density and cell proliferation [8].

Cerebellar haemangioblastomas are histopathologically benign but a degree of malignant clinical behaviour is found in long-term follow-up (as observed in the mother and the maternal aunt of our young patient). They have recently been reviewed by the French VHL group [9]: on 18 supratentorial haemangioblastomas in 13 patients, each with an identified VHL germline mutation, temporal sites were the most common. Of 14 tumours with documented serial imaging, 13 demonstrated tumour growth with formation of cysts. They may proliferate again even after total resection of the primary tumour [10]. Haemangioblastomas of the pituitary stalk have also been described [11] but we could not find any published description of a pituitary adenoma in VHL disease even though some unreported cases might exist (prolactinoma in a 32-year-old French woman according to SR).

Pituitary adenomas are rare in children: approximately 3.5 to 8.5% of all pituitary tumours are diagnosed before the age of 20 years [12]. The majority of these tumours are sporadic, but in children, they can be part of a genetic condition predisposing to pituitary and other tumours such as GNAS, menin, PRKAR1A, AIP and p27 (CDKN1B) mutations [12]. VHL disease might be added to these genetic diseases if other cases are reported. Prolactinomas account for approximately 50% of pituitary adenomas and are the most common pituitary adenomas in older children. Treatment with dopamine agonists is recommended since they have both antisecreting and antiproliferative properties. Growth and pubertal retardation are often observed [12]. Despite the family pressure, we felt it unsafe to prescribe substitutive GH treatment for this young patient.
Table 1
Subclassification of VHL disease (4).

<table>
<thead>
<tr>
<th>VHL subtype</th>
<th>Tumour risk: renal cell carcinoma</th>
<th>Tumour risk: haemangioblastoma of central nervous system</th>
<th>Tumour risk: phaeochromocytoma</th>
<th>Mutation type</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Whole or partial gene deletion or non-sense mutation</td>
</tr>
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<td>High</td>
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<td>Missense mutation</td>
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GH-secreting pituitary adenomas account for approximately 5–15% of paediatric pituitary adenomas in children and adolescents before the age of 20 years [12]. They are mainly macroadenomas that can be treated by transnasal surgery. Growth hormone-secreting pituitary adenomas in childhood and adolescence are more likely to be invasive or aggressive [13]. Nevertheless, we hypothesize that pituitary adenomas discovered in VHL patients might be particularly aggressive. Some authors have reported that pituitary tumours may be highly invasive in younger patients [1]; however, others did not report similar findings [3].

Increased angiogenesis is well-established in VHL, and clinical trials of antiangiogenic therapy (anti-VEGF) are currently being performed in such patients [14]. Immunohistochemistry studies of the expression of VEGF were recently published for 56 patients with GH-secreting pituitary adenomas before surgery, both treated (octreotide, n = 33, bromocriptine, n = 11) and not treated [15]. Diffuse cytoplasmic VEGF staining was strongly positive in normal pituitary glands. Moderately positive staining with VEGF occurred in six of 33 (18%) cases in the octreotide-treated group and in eight of 12 (67%) cases in the control group. As octreotide has been shown to decrease VEGF expression in GH-secreting pituitary adenomas [15], we have used this drug to improve control of tumour progression after stereotaxic irradiation. Stereotaxic radiotherapy was performed because the second attempt at surgery could not excise all affected tissue. Radiotherapy, whether primary or post-surgery, has a slow onset therapeutic effect. We, therefore, preferred to maintain medical treatment. Temozolomide has recently been shown to be an effective treatment for aggressive pituitary tumours [16]. If there is progression of the residual tumour tissue in this young patient, we will finally use this treatment.

Genetic testing confirmed that the patient had the VHL mutation previously identified in his family (p.Gly114Arg), and this has only been reported in one other family to date considering different database [17–19]. The VHL gene has three exons that encode the VHL-P. VHL is a tumour suppressor protein that is located in the nucleus or cytoplasm, the extent to which it is secreted being dependent on cell density. Abnormal or absent VHL-P function might disrupt tumour suppression indirectly through HIF-mediated effects or directly through VHL-mediated effects, or both [2].

The pattern of tumour types that develops in a VHL-affected family defines the clinical subtype (1, 2A, 2B, 2C) (Table 1). Generally, it is difficult to predict accurately an individual’s clinical phenotype on the basis of his VHL mutation.

In conclusion, VHL mutation favours the development of various types of tumour in an affected subject. In our case, besides multiple haemangioblastomas, the patient had a pituitary macroadenoma that is not usually observed in VHL disease. The choice of appropriate treatment continues to be an important issue for this patient, the purpose being to extend his life expectancy without affecting his quality of life.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


