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Adenomas Pituitary in Children And Adolescents

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Summary: *Pituitary tumors are rare in childhood and adolescence, with a reported prevalence of up to 1 per million children. Although pituitary tumors are rare in childhood and adolescence, and are typically histologically benign, significant morbidity may result due to their location, mass effect, and/or interference with normal pituitary hormone functions. The frequency of macro adenomas and aggressive forms reflects the difficulty of their management. The treatment is superimposable to what is done in adults. Genetic impairment is more frequent and should be discussed systematically.*
We report in this study phenotypic and genotypic characteristics of pituitary adenomas in 16 children hospitalized in our department of endocrinology
Keywords: *macroadenoma, headache,growth failure , disturbance of pubertal development , genetic mutation*

I. Introduction

Pituitary tumors are rare in childhood and adolescence, with a reported prevalence of up to 1 per million children. Only 2 - 6% of surgically treated pituitary tumors occur in children. Although pituitary tumors in children are almost never malignant and hormonal secretion is rare, these tumors may result in significant morbidity due to the interference with endocrine function during a vulnerable period of development. Tumors within the pituitary fossa are of two types mainly, craniopharyngiomas and adenomas (1). Common presenting signs of adenomas are headache, visual disturbances , growth failure or disturbance of pubertal development. The majority of pituitary tumors are sporadic. However they are sometimes seen in association with genetic conditions such as MEN1, Carney complex, familial acromegaly and McCune Albright syndrome (2).

The objective of this study is to report phenotypic and genotypic characteristics of pituitary adenomas in children

II. Population, Methodology

It is a retrospective study of sixteen children (n: 13) and adolescents (n: 3) with a pituitary adenoma diagnosed and followed between 2000 and 2016. All patients received a full clinical examination, an hormonal assessment (Hypophysiogram) , Imaging of the hypothalamohypophyseal region in magnetic resonance (H-HMRI), a neurophthalmological assessment and a genetic study in search of a mutation of the gene Menine, AIP and FIPA. At the end of the exploration, a therapeutic decision was indicated according to the etiological exploration: Medical treatment and or neurosurgery. Clinical and paraclinic post-therapeutic re-evaluation is performed (hypophysiogram, H-HMRI) systematically. Depending on the results, a simple monitoring or therapeutic complement is decided. All the surgical specimens were studied histologically and immunohistologically.

III. Results

Average age was 8,6 ± 0.4 (6-17) years . Prolactin adenoma was observed in the peripubertal period (12.4 ± 0.2), the other adenomas were observed at a younger age:

Corticotropic adenomas (8.4 years), somatotropic adenomas (7 years), non-functional adenomas (10 years). The Sex ratio F / G is 1.5. Tumor syndrome is constant with ophthalmological disorders in 70% and gigantism in two cases. The causes were dominated by hypersecreting adenomas (81.2%). Prolactin adenomas are the most frequent (37.5% (Table I)

Table I: Distribution of patients according to type of adenoma

Adénoma	Number	%
Prolactinoma	6	37,5
Cushing disease	4	25
Somatotropic adenoma	3	18,7
Non fontionning adenoma	3	18,7

The tumor lesion is large in all cases: mean tumor height: 26 mm ± 0.8 (18-45). Three patients had a giant adenoma. All the procedures were invasive macroadenomas with the exception of cushing disease which consisted only of microadenomas (mean size 3.4 mm).

Endocrine evaluation revealed dissociated anterior pituitary insufficiency in all patients. The somatotropic deficit is constant except for cases of somatotropic adenomas. The thyrotropin deficiency is observed in half of the cases. No central insipid diabetes was observed. The genetic investigation revealed NEM 1 n: 4. The search for the AIP gene and FIPA was negative for the other cases.

From a therapeutic point of view, medical treatment with dopaminergic analogs (Cabergoline) has been instituted in patients with prolactinoma. No side effects was observed. Hormonal and neuroradiological controls showed a tumoricidal and antisecretory effect in all cases with a mean tumor volume reduction of 40% after an average treatment time of 1.5 ± 0.2 years.

Surgery in other cases was not successful, however an improvement in ophthalmologic disorders was noted in all cases. Resection was partial (average 30% reduction) requiring further treatment: somatostinergiques agonists and radiotherapy in somatotropes adenomas, dopamine agonists + agonists somatostatinergic + radiotherapy in non-functional adenomas. The various treatments surgeries, radiotherapy have generated other endocrine deficits (Deficits thyreotrope, gonadotropic, corticotropic: n: 10/10); Tumor stabilization was observed after an average follow-up of 6 years.

In the case of corticotropic adenomas, excision has achieved remission in 50% of cases. In the other half, anti-cortisol treatment + radiotherapy was indicated. Given the persistence of hypercortisolism in one case, a bilateral adrenalectomy is business. No mortality cases were observed

IV. Discussion

Pituitary adenomas are rare in children and adolescent; They represent 3% of intracranial tumors (1). The majority of these tumors are sporadic, but in children, more common than in adults, they can be part of a genetic condition predisposing to pituitary and other tumors. Nevertheless, even sporadic tumors harbor significant genetic abnormalities: most pituitary tumors are monoclonal lesions and modifications in expression of various oncogenes or tumor suppressor genes, including *GNAS, PTTG, HMGA2,* and *FGFR-4* have been identified (3)(4) Prolactinomas account for approximately 50% of pituitary adenomas. They are the most common pituitary adenomas in older children, with the majority occurring in adolescence with a female preponderance in older children and adolescents. Prolactinomas may be seen in several inherited syndromes, including MEN 1, Carney complex, and familial isolated pituitary adenomas . A pituitary adenoma may be the first clinical manifestation of MEN 1 (5)(6)(7)

Among functional pituitary tumors in early childhood, ACTH-producing adenomas are probably the most common although they are still considerably rare. To date, no genetic defects have been consistently associated with childhood corticotropinomas, which only rarely occur in the familial setting, and then, most commonly in the context of multiple endocrine neoplasia type 1 (MEN 1) (8)

GH- and/or PRL-producing are the second most frequently found functional pituitary tumors in early childhood; these tumors in children almost always occur in the familial setting or in the context of known genetic defects:*GNAS, menin, PRKAR1A, AIP* and p27 (*CDKN1B*) mutations . Somato- and/or mammotropinomas become significantly more frequent than corticotropinomas in late childhood, adolescence and adulthood (3).

Some authors reported that pituitary tumors may be highly invasive in younger patients ; However, others did not report similar findings (9).

Clinical presentation varies depending on the age and gender of the child, although growth arrest is typically seen in children and adolescents before ephiphyseal fusion is completed. Females may present with pubertal delay, amenorrhea, and other symptoms of hypogonadism. In males, macroprolactinomas are more frequent; accordingly, males with prolactinomas also have a higher incidence of neurological and opthalmological abnormalities (i.e. cranial nerve compression, headaches, visual loss), growth or pubertal arrest and other pituitary dysfunctions. Contrary to common belief, gynecomastia is not a common finding (9).

Medical management with dopamine agonists (e.g. bromocriptine, pergolide, or cabergoline) is typically the first line of treatment for prolactinomas. The goals of treatment include the normalization of prolactin levels and pituitary function and the reduction of tumor size. Dopamine agonists are effective in reducing tumor size and controlling prolactin levels in approximately 80-90 % of patients with microadenomas and about 70% of macroadenomas . Studies report that cabergoline, a selective D2 receptor agonist, is more effective and often better tolerated than bromocriptine. In addition, cabergoline has been shown to be effective in treatment of tumors resistant to other dopamine agonists . In some cases treatment with dopaminergic agents can be withdrawn and PRL levels will remain within normal limits .

Surgical intervention for prolactinomas is reserved for emergency situations such as acute threat to vision, hydrocephalus, or cerebral spinal fluid leak, or for these rare tumors that grow despite exposure to

increasing doses of dopamine agonists. Compliance is often a problem in long-term management of prolactimonas, since cessation of medical treatment leads to recurrence of hyperprolactinemia and tumor re-growth (10)(11) (12).

Corticotropinomas are the most common pituitary adenomas in prepubescent children; their frequency decreases during puberty and in adolescence, when prolactinomas become more prevalent. The cumulative incidence of ACTH-producing tumors or Cushing disease in children does not exceed a tenth of the annual incidence of 2-5 new cases of Cushing syndrome per million people per year (13) (14).

The most characteristic clinical presentation of Cushing disease is that of significant weight gain concomitant with severe failure to gain in height. Other common symptoms include headaches, hypertension, glucose intolerance, and delayed pubertal development and amenorrhea despite often significant virilization and hirsuitism. Compared to adults and older adolescents, children and younger adolescents do not typically report problems with sleep disruption, muscle weakness, or problems with memory or cognition.

Corticotroph adenomas are significantly smaller than other types of pituitary tumors (usually 3 mm or less). Rarely, first-line treatment for Cushing disease in childhood is always surgical; transsphenoidal adenomectomy or hemihypophysectomy in situations where the surgical exploration is negative has been shown to be nearly 90% curative. Radiation or gamma-knife therapy is reserved for these patients in whom surgical intervention failed . Bilateral adrenalectomy may be considered for inoperable or recurrent cases; however it is associated with a significant risk of development of Nelson's syndrome (14)(15)

Somatotropinomas comprise approximately 5-15% of pediatric pituitary adenomas in children and adolescents before the age of 20 years. Excess GH production results from an adenoma, usually macroadenoma or, rarely, somatotroph hyperplasia which occurs in certain genetic conditions such as McCune-Albright syndrome or Carney complex. GH excess due to dysregulation of GHRH signaling may occur as a result of a local mass effect, for example with optic glioma seen in neurofibromatosis type-1 (NF-1) (16) or (almost unheard of in children) from an ectopic GHRH-producing tumor. These tumors may also stain for prolactin and thyrotropin, which is usually of no clinical significance. Clinical presentation in children and adolescents varies depending on whether the epiphyseal growth plate is open. Prior to epiphyseal fusion, significant acceleration of growth velocity is noted, a condition also known as `gigantism'; as epiphyseal fusion is completed, the clinical symptoms become more similar to those in acromegalic adults (coarse facial features, broadened nose, large hands and feet, obesity, organomegaly, sweating, nausea). Since somatotropinomas are often macroadenomas, headaches and visual disturbances are frequently reported (16)(17) .

First-line of treatment for childhood gigantism or acromegaly is transsphenoidal surgery; however, unlike Cushing disease, GH-producing tumors are often large and locally invasive. With small, well-circumscribed tumors transspheniodal surgery may be curative, while with larger and locally invasive tumors surgery may be beneficial to decompress tumors but persistent or recurrent disease is common and adjuvant therapy is needed. Radiotherapy, either primary or post-surgical, has slow onset of treatment effect and high treatment related morbidity of panhypopituitarism (18) (19).

Pharmacologic agents are often indicated both before and after surgery and have been shown to be effective at shrinking tumor size and improving biochemical abnormalities. Long-acting somatostatin analogs have been shown to be effective at normalizing IGF-1 levels in most patients (20)(21)(22) . Non-functioning pituitary tumors in childhood and adolescence are rare; these tumors represent only 4 to 6% of pediatric cases while in series of adult patients, hormonally silent tumors account for approximately 33 to 50% of the total number of pituitary lesions (23)(24). Most silent adenomas arise from gonadotroph cells and often are macroadenomas at diagnosis; they occasionally grow and may present with headaches and visual disturbances, as well as deficient growth and/or pubertal delay (25). Large adenomas may obstruct the foramen of Monro and cause hydrocephalus, while pituitary adenomas and sellar tumors that impinge on the optic apparatus and/or cavernous sinus can result in cranial nerve palsies, cavernous sinus syndromes, and/or additional visual disturbances. Nonfunctioning pituitary adenomas may present with GH deficiency (up to 75%), LH/FSH deficiency (~40%), or ACTH and TSH deficiency (~25%) . Compression of the pituitary stalk by pituitary adenoma has been reported but secondary hyperprolactinemia is typically seen in less than 20% of patients. DI is also rare (9 to 17%) (26) .

V. Conclusion

Although pituitary tumors are rare in childhood and adolescence, and are typically histologically benign, significant morbidity may result due to their location, mass effect, and/or interference with normal pituitary hormone functions. La Fréquence des macro adénomes et des formes agressives rend compte de la difficulté de leur prise en charge. Le traitement est superposable à ce qui est fait chez l'adulte. L' atteinte génétique est plus fréquente et doit etre évoqué systématiquement.

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