

Advances in the diagnosis, treatment and molecular genetics of pituitary tumors in childhood

Constantine A. Stratakis, MD, D (Med) Sci.

Section on Endocrinology Genetics, Program on Developmental Endocrinology Genetics (PDE-GEN), Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), National Institutes of Health (NIH), Bethesda, MD20892, USA.

Abstract

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, with some variation attributed to a lack of consensus for a pediatric age range and whether age at surgery or age at onset of symptoms was used. Although pituitary tumors in children are almost never malignant and hormonal secretion is rare, these tumors may result in significant morbidity. Pituitary adenomas produce a variety of hormonal conditions such as hyperprolactinemia, acromegaly or gigantism, or Cushing disease. Sporadic lesions comprise the majority of pituitary tumors in children and there is sparse information about genetic causes. However, in children more frequently than in adults, pituitary tumors may be a manifestation of genetic conditions such as Carney complex, McCune-Albright syndrome, multiple endocrine neoplasia type 1 (MEN 1), and familial isolated pituitary adenoma (FIPA). The study of pituitary tumorigenesis in the context of these genetic syndromes has advanced our knowledge of the molecular basis of pituitary tumors and may lead to new therapeutic developments. Molecular understanding of pituitary adenoma formation is essential for the development of medical therapies and the treatment of post-operative recurrences. In general, mutations in genes involved in genetic syndromes associated with pituitary tumors are not a common finding in sporadic lesions. In contrast *MEN1* and

AIP mutations may be more frequent among specific subgroups of patients, such as in children and young adults with growth hormone-producing adenomas. In this presentation, we review the most recent data on clinical diagnosis and outcomes, as well as in the molecular pathogenesis of pituitary adenomas and discuss some of the most recent findings from our laboratory. Guidelines for genetic screening and clinical counseling of patients with pituitary tumors are provided.

Keywords: Pituitary adenomas, familial syndromes, molecular pathways, clinical picture, multiple endocrine neoplasia, genetics.

Introductory notes

The pituitary gland has an essential role in the maintenance of homeostasis, normal growth, and reproductive function. Although pituitary tumors are rare in childhood and adolescence, and typically histologically benign; significant morbidity may result due to their location, mass effect, and/or interference with normal pituitary hormone functions. ⁽¹⁾ Early identification of pituitary tumors in children is necessary to avoid serious adverse effects on both physiological and cognitive outcomes as a result of pituitary hormone dysregulation during the critical periods of growth in childhood and adolescence. In this report, we review recent findings on the diagnosis, evaluation, treatment, and molecular genetics of pituitary adenomas presenting in childhood.

Pituitary adenomas

Overview

Due to the rarity of pituitary tumors in children and adolescents, accurate information regarding the prevalence and incidence of pituitary tumors is lacking. Data from autopsy studies (primarily adults)

Correspondencia:

Constantine A. Stratakis, MD, D (Med) Sci, SEGEN, PDEGEN & Pediatric Endocrinology Program, NICHD, NIH, Building 10, CRC (East Laboratories), Room 1-3330, 10 Center Dr., MSC1103, Bethesda, Maryland 20892, USA.
Tel. 301-496-4686/496-6683, fax 301-301-402-0574/480-0378, e-mail: stratakoc@mail.nih.gov

show that pituitary adenomas develop in approximately 17-25% of the population. ^(1, 2) In addition, studies with radiological imaging report a similar incidence of pituitary gland lesions in the general population (up to 20%) with no gender predilection. ⁽³⁾ Approximately 3.5 to 8.5% of all pituitary tumors are diagnosed prior to the age of 20 years and they account for approximately 3% of all diagnosed intracranial tumors in childhood ⁽⁴⁻⁸⁾.

The majority of pituitary tumors are sporadic; however in children more commonly than in adults, they can be part of a genetic condition predisposing to pituitary and other tumors. However, even sporadic tumors may 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. ^(9, 10) Pituitary tumor development and cell growth are likely influenced by both pituitary and hypothalamic factors. ^(1, 11, 12) Other factors and genetic events seem to be implicated in pituitary cell clonal expansion, and oncogene activation is necessary to propagate tumor growth. ^(9, 13) An example of this secondary phenomenon is the widespread presence of GNAS activating mutations in sporadic GH-secreting pituitary tumors (in up to 40% of all such lesions).⁽¹⁴⁾

ACTH-producing adenomas are probably the most common functional pituitary tumors in early childhood, although they are still considerably rare. 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). ⁽¹⁵⁻¹⁷⁾

The second most frequently found functional pituitary tumors in early childhood are GH- and/or PRL-secreting, and these tumors in children occur almost always in the familial setting or in the context of known genetic defects: GNAS, *menin*, *PRKAR1A*, *AIP* and *p27 (CDKN1B)* mutations. ^(6, 18-22) In late childhood, adolescence and adulthood somatotrophic and/or mammatropinomas become significantly more frequent than corticotropinomas.⁽²³⁾

Corticotropinomas

The most common type of pituitary adenomas in prepubescent children are corticotropinomas; however the frequency decreases during puberty and in late adolescence, when the incidence of prolactinomas becomes more prevalent. The cumulative incidence of corticotropinomas (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. ^(7, 24, 25) Typically, corticotroph ade-

nomas are significantly smaller than other types of pituitary tumors (usually 3 mm or less). Rarely, they can be exophytic, growing into the subarachnoid space, or invade the cavernous sinus or wall. In addition, there are case reports of tumors that originate in the posterior lobe. ⁽²⁶⁾

Clinical presentation, evaluation, and treatment

In children, the most characteristic clinical presentation of Cushing disease (CD) is significant weight gain concomitant with a decrease in linear height velocity. Other typical symptoms include headaches, delayed pubertal development and amenorrhea (despite significant virilization and hirsutism), hypertension, and glucose intolerance. Children and younger adolescents usually do not report problems with sleep disruption, muscle weakness, or problems with memory or cognition, compared to older adolescents and adults with Cushing disease. ⁽²⁶⁾

Our group recently suggested a 3-day inpatient evaluation of children suspected of having Cushing syndrome for confirmation of the diagnosis and investigation of a corticotropinoma. ⁽²⁷⁾ A midnight serum cortisol value of 4.4 ug/dL confirmed the diagnosis of Cushing syndrome in all children (sensitivity of 99% and specificity of 100%). Morning corticotropin levels were elevated in patients with CD (median of 18 pg/mL); a cutoff value of 29 pg/mL had 100% specificity and 70% sensitivity. A decrease in morning cortisol of 20% with the high dose overnight dexamethasone suppression test (120 ug/kg, maximum dose 8 ug) provided the highest sensitivity (97.5%) in differentiating CD from primary adrenal disorders. MRI of the pituitary gland identified a lesion in 63% and CT imaging of the adrenals showed bilateral adrenal hyperplasia in 53% of children with CD. Bilateral inferior petrosal sinus sampling is usually reserved for patients with confirmed ACTH-dependent CS and a negative pituitary MRI; or in situations where there is inconsistency in the biochemical data and the MRI is suggestive of a pituitary lesion, to exclude an ectopic source of ACTH production. Our group recently reported that in an experienced center, BIPSS was safe; however lateralization of the ACTH gradient during BIPSS is a poor predictor of lateralization of the tumor. ⁽²⁸⁾

Recent studies report the use of post-contrast spoiled gradient-recalled acquisition (SPGR) in the steady state in addition to conventional T-1 weighted spin echo (SE) acquisition MRI. ^(29, 30) SPR-MRI was superior to conventional MRI imaging for the diagnostic evaluation of corticotropinomas and, in general, for investigation of the pituitary gland in children and adults.

Transphenoidal adenomectomy or hemihypophysectomy is considered first-line treatment for CD

in childhood and adolescence. Hemihypophysectomy has been shown to be nearly 90% curative in situations where the surgical exploration is negative. In situations when surgical intervention has not been successful, radiation or gamma-knife therapy is the next line of treatment. ^(24, 26) An option for inoperable or recurrent CD is bilateral adrenalectomy; however it is associated with a significant risk of development of Nelson's syndrome. ^(31, 32)

Prolactinomas

Prolactinomas account for approximately 50% of pituitary adenomas overall and are the most common pituitary adenomas in adolescents, with a female preponderance ⁽³³⁻³⁶⁾. Prolactinomas may be seen in several inherited syndromes, including MEN 1, Carney complex, and familial isolated pituitary adenomas. ⁽³⁷⁾

Clinical presentation, evaluation, and treatment

The clinical presentation of prolactinomas varies depending on the age and gender of the child. Growth arrest is typically noted in children and adolescents prior to epiphyseal fusion. Macroprolactinomas are found more frequently in males, perhaps due to lower detection rates during the initial phase of tumor development. Consistent with a later diagnosis and larger tumor size, males with prolactinomas also have a higher incidence of neurological and ophthalmological abnormalities (i.e. cranial nerve compression, headaches, visual loss), growth or pubertal arrest and other pituitary dysfunctions. Gynecomastia is not a common finding. Females may present with pubertal delay, amenorrhea, and other symptoms of hypogonadism. The differential diagnosis includes various factors such as neurogenic or mechanical processes that can result in loss of dopaminergic suppression of pituitary lactotrophs and resultant hyperprolactinemia, such as mass effects from craniopharyngiomas, Rathke cleft cyst, nonfunctioning adenomas, or an infiltrative process. ⁽³⁸⁾

The diagnosis of prolactinoma is based on measurement of serum prolactin levels (indwelling line, patient resting and fasting for an hour) and neuro-radiological imaging. Basal prolactin levels of greater than 200 ug/L are diagnostic, whereas levels between 100-200 ng/mL and the presence of a mass, requires additional investigation to rule out mass effect versus a prolactinoma. Waas (2006) reported that all but one patient in a series of 223 with non-functioning adenomas had prolactin levels less than 100 ng/mL, which provides a well-defined cutoff value for clinical management. ⁽³⁹⁾

The first line of treatment for prolactinomas is medical management with dopamine agonists (e.g. bromocriptine, pergolide, or cabergoline),

with the goals of normalization of prolactin levels and pituitary function and the reduction of tumor size. Dopamine agonists have demonstrated effectiveness in reducing tumor size and controlling prolactin levels in approximately 80-90% of patients with microadenomas and about 70% of macroadenomas. ⁽⁴⁰⁾ Cabergoline, a selective D2 receptor agonist, is more effective and often better tolerated than bromocriptine, and has been shown to be effective in treatment of tumors resistant to other dopamine agonists. ⁽⁴¹⁾ For some patients treatment with dopaminergic agents can be withdrawn and PRL levels will remain within normal limits. ⁽⁴²⁾

Patient compliance is often a problem in long-term management of prolactinomas. Commonly reported side effects of dopamine agonist treatment include nausea, dry mouth, dyspepsia, or dizziness at the initiation of therapy. ^(43, 44) Cessation of medical treatment leads to recurrence of hyperprolactinemia and tumor re-growth. Treatment doses of 2.5 to 10 mg daily (bromocriptine) or 0.25 to 2 mg weekly (cabergoline) have not been associated with long-term adverse effects.

Recent reports in the New England Journal of Medicine 45-47 of cardiac valve regurgitation in patients treated with long-acting dopamine agonists have raised concerns about the safety of these medications. The safety of cabergoline was evaluated in a nested case-control study of patients in the UK general practice database and a study of 1200 patients with Parkinson's disease (controlled and uncontrolled studies at doses of up to 11.5 mg/day, which exceed the maximum recommended dose for treatment of hyperprolactinemic disorders). The risk of valvular disease appeared to be higher in patients treated with at least 3 mg per day of cabergoline, a dose that is 10 to 20 times higher than the standard regimen for macroprolactinomas. Discussion of potential risks of therapy with the patient and decision about the need for echocardiogram is advisable.

Recently, Kars *et al.* (2008) reported a cross-sectional study of patients with prolactinomas who received cabergoline treatment (mean 5.2 years, range 1-10.3 years) and noted an increased prevalence of aortic valve calcification with mild tricuspid regurgitation; but not clinically relevant valvular heart disease. ⁽⁴⁸⁾ Discussion of potential risks of therapy with the patient and decision about the need for echocardiogram is advisable.

Urgent situations, such as acute threat to vision, hydrocephalus, or cerebral spinal fluid leak, or for the rare tumors that grow despite exposure to increasing doses of dopamine agonists may require surgical intervention. ^(49, 50)

Somatotropinomas

Prior to the age of 20 years, somatotropinomas account for approximately 5-15% of pediatric pituitary adenomas. Typically, the excess GH production results from an adenoma (usually macroadenoma); however, somatotroph hyperplasia may be a rare cause of excess GH that can occur in certain genetic conditions such as McCune-Albright syndrome or Carney complex. 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) and result in GH excess,⁽⁵¹⁾ or from an ectopic GHRH-producing tumor, which is almost unheard of in children.

Clinical presentation, evaluation, and treatment

The clinical presentation of somatotropinomas 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'. When epiphyseal fusion nears completion, 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, mass effects, such as headaches and visual disturbances are frequently reported.^(52, 53)

Diagnosis is confirmed by elevated IGF-1 level, failure to suppress GH during oral glucose tolerance test (1.75 g/kg), elevated IGFBP3 level, and neuroradiology imaging (MRI). Assessment of pituitary function should include cosyntropin stimulation test, thyroid panel, gonadotropin, and prolactin measurement.

Transsphenoidal surgery is the first-line of treatment for childhood gigantism or acromegaly; however, unlike Cushing disease, GH-producing tumors are often large and locally invasive. Transsphenoidal surgery may be curative with small, well-circumscribed tumors; while larger and locally invasive tumors may benefit from surgical decompression; however, 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.^(6, 54-56)

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.⁽⁵⁶⁻⁶²⁾ However, since treatment with long-acting somatostatin analogs suppresses insulin secretion, this may increase the risk for development of glucose intolerance.^(63, 64)

A GH receptor antagonist, pegvisomant, has demonstrated effectiveness for normalization of IGF-1 levels with no detrimental effects on glucose metabolism.^(65, 66) Pegvisomant, on the other hand, requires a daily injection, an important factor to be considered when initiating this type of treatment. A study of the long-term efficacy and safety of combination therapy (long-acting somatostatin analog plus twice weekly pegvisomant) reported that IGF-1 levels normalized for all patients (n=32); however, transient elevation in liver enzymes was observed in eleven patients, with a higher risk for patients diagnosed with diabetes mellitus. Combination therapy can offer an additional benefit since tumor suppression activity is combined with GH receptor blockade⁽⁶⁶⁾. There is limited data on pegvisomant treatment in children, mostly case studies, which report successful outcome.^(67, 68)

Incidentally discovered pituitary adenomas in childhood are rare, since overall non-functioning pituitary tumors in childhood and adolescence are rare. Hormonally silent tumors represent only 4 to 6% of pediatric cases while in series of adult patients, they account for approximately 33 to 50% of the total number of pituitary lesions.^(5, 69, 70) Most non-functioning adenomas arise from gonadotroph cells and often are macroadenomas at diagnosis; they may present with headaches and visual disturbances, as well as growth and/or pubertal delay⁽⁷¹⁾. Large adenomas may 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. Hormonally silent adenomas may present with GH deficiency (up to 75%), LH/FSH deficiency (~40%), or ACTH and TSH deficiency (~25%).⁽⁷¹⁾ Although compression of the pituitary stalk by pituitary adenoma has been reported; secondary hyperprolactinemia is seen in less than 20% of patients. Diabetes insipidus is also rare (9 to 17%) but is more commonly seen in patients with Rathke's cleft cysts⁽³⁴⁾. Recommendation for surgical excision of a hormonally silent intrasellar tumor or cyst depends on the tumor size, location, and potential for invasiveness.

Molecular genetics of pituitary tumors

Four genetic conditions associated with pituitary tumors include: Carney complex (CNC), McCune Albright syndrome (MAS), multiple endocrine neoplasia type 1 (MEN1), and familial isolated pituitary adenomas (FIPA) provide useful models to advance our knowledge of the molecular basis of pituitary tumors. In the remaining text of this report we briefly review these conditions.

Carney complex

First described by Carney in the mid-1980s, Carney complex is a rare autosomal dominant disorder that

includes a complex of endocrine overactivity, lentiginos, myxomas, and other tumors such as schwannomas and/or pituitary adenomas. Genetic defects in one of the regulatory subunits of protein kinase A (PKA) (regulatory subunit type 1 alpha, PRKAR1A) causes CNC.72. An inactivating mutation in the gene encoding PRKAR1A has been identified in approximately 60% of patients who met the diagnostic criteria and a second, as yet uncharacterized locus at 2p16 has been implicated in some families.⁽⁷³⁾

Pituitary pathology has been described in a number of studies of patients with CNC and includes hypersomatotropinemia and hyperprolactinemia, which often begin in adolescence. Acromegaly in CNC is characterized by a slow progressive course and aggressive pituitary tumors are not common. However, in many patients clinically significant acromegaly did not manifest until after surgical treatment of their Cushing syndrome (72% of these patients were diagnosed with CS due to primary pigmented nodular adrenocortical disease), which is not surprising given the known relationship between cortisol and growth hormone.⁽²⁰⁾

It is important to identify clinically significant acromegaly as defined by generally applied criteria for patients with CNC who have elevated GH and/or IGF-1⁽⁵⁶⁾. It is not uncommon for CNC patients to have an abnormality of GH secretion due to the underlying pituitary hyperplasia, however almost all will have negative imaging studies.^(72, 74) For CNC patients with elevated IGF-1 levels treatment with somatostatin analogues with the goal of normalizing IGF-1 is recommended.^(72, 75) For CNC patients with normal IGF-1 levels and normal pituitary imaging, but with abnormal response to oral glucose tolerance test, evaluations should be performed annually to assess for changes that may require treatment.

McCune Albright syndrome

McCune Albright syndrome (MAS) is a genetic (but not inherited -90) disorder characterized by polyostotic fibrous dysplasia, café-au-lait pigmented lesions, endocrine abnormalities (precocious puberty, thyrotoxicosis, pituitary gigantism, and Cushing's syndrome) and rarely other tumors. Somatic mutations on the adenylate cyclase-stimulating G alpha protein (GNAS complex locus, GNAS) are found in McCune Albright syndrome.⁽⁷⁶⁾ GNAS maps to chromosome 20 q⁽¹³⁾ and encodes the ubiquitously expressed Gs- α subunit of the G protein. The activation of adenyl cyclase signaling pathways results in the phenotype of MAS including hypersomatotropinemia. GNAS mutations have also been identified in sporadic GH-producing tumors.

Similar to patients affected by CNC or carriers of PRKAR1A mutations, GH excess in MAS is commonly found (approximately 20% of the patients)

but pituitary tumors are not typically detectable by MRI.^(77, 78) However, elevated GH levels in patients with MAS may be associated with significant morbidity due to exacerbation of polyostotic fibrous dysplasia.^(79, 80) Hypersomatotropinemia has also been implicated in sarcomatous transformation of bone tumors in a MAS patient.⁽⁸¹⁾ Similar to patients with CNC, GH- and PRL- producing cell hyperplasia are common histological findings in the pituitary.^(18, 79, 82)

Treatment of GH- producing tumors in MAS with cabergoline has consistently shown an inadequate response; while long-acting octreotide has demonstrated an intermediate response. Recently, GH-receptor antagonists have been proposed as effective medical intervention for patients with inoperable MAS pituitary tumors or hypersomatotropinemia without a visible tumor.^(59, 62, 83)

MEN1 is a disorder characterized by a predisposition to peptic ulcer disease and primary endocrine hyperactivity involving the pituitary, parathyroid, and pancreas, which is inherited in an autosomal dominant manner. The disorder is due to inactivating mutations in the menin gene, a tumor suppressor, which has been localized to chromosome 11q⁽¹³⁾. Studies report that menin interacts with various proteins involved with transcriptional regulation, genome stability, cell division and proliferation.^(15, 16, 84, 85)

Pituitary adenomas are found in approximately 30 to 40% of patients with menin mutations, most commonly PRL (~60%) and GH (~20%) secreting; while ACTH-secreting and non-functional adenomas represent less than 15% of MEN 1-associated pituitary adenomas.^(15, 34) The frequency of pituitary disease is significantly higher in familial *versus* sporadic MEN⁽¹⁾ cases, although no genotype-phenotype correlation has been noted in menin mutation carriers.⁽¹⁵⁾ In addition, an increased female-to-male ratio has been reported in MEN⁽¹⁾ patients with pituitary adenoma and acromegaly for both familial and sporadic cases.⁽¹⁾ A pituitary adenoma may be the first clinical manifestation of MEN⁽¹⁾, with the youngest reported case in a 5-year old boy with a pituitary somatomammotroph macroadenoma.⁽⁸⁶⁾

Familial isolated pituitary adenomas (FIPA) is a clinical condition that refers to kindreds with two or more pituitary adenomas that are genetically negative for mutations in menin or PRKAR1A. Homogeneous mutations refer to similar pituitary tumor type occurring within the same family and heterogeneous mutations refer to families with two or more different tumor types.⁽²²⁾ All pituitary tumor phenotypes have been reported in FIPA kindreds, and typically at least one prolactin- or GH-secreting adenoma is noted in each family.

Vierimaa (2006) reported that inactivation mutations of the gene encoding aryl hydrocarbon receptor-

interacting protein (AIP) were found in patients with pituitary tumors (typically acromegaly) in both sporadic and familial settings.⁽⁸⁷⁾ A genome-wide and DNA mapping study recently identified inactivating mutations in the AIP gene on chromosome 11q13.3. In this series, combinations of somatotropinomas, prolactinomas, and mixed GH- and PRL-secreting adenomas, and were reported. Lack of functional AIP was shown by loss of heterozygosity in the tumor FIPA specimens. AIP mutations were noted in 15% of FIPA families and half of those with isolated familial somatotropinoma, which is a well-described clinical syndrome related only to patients with acrogigantism. Tumors in patients with AIP mutations are usually larger and diagnosed at a younger age than patients without AIP mutations or in sporadic tumors.^(88, 89) Familial growth hormone secreting pituitary adenomas may occur as an isolated autosomal dominant disorder (familial somatotropinoma)^(90, 91) or as part of MEN 1 and Carney complex.^(18, 92)

Conclusions

Significant improvements in the diagnosis and interventions for pituitary tumors in childhood and adolescence have resulted from advances in diagnostic testing, neuroimaging, microneurosurgery, and pharmacological interventions. Genetic syndromes such as CNC, MAS, MEN1, and familial isolated pituitary adenomas, have provided insight into the molecular basis of pituitary tumors and provide a basis for future research on molecular mechanisms of genesis of endocrine tumors. Treatment of rare disorders, such as pediatric pituitary tumors, requires a multidisciplinary team with expertise in the diagnosis, treatment, and long-term management of this disorder to facilitate early diagnosis and treatment and reduce morbidity. The family of a child diagnosed with a pituitary tumor as part of a genetic syndrome should be offered genetic counseling and surveillance of family members as appropriate. As ongoing studies identify gene and protein expressions, mutations, and candidate genes important for the development and function of the anterior pituitary gland, this information will facilitate earlier diagnosis and provide opportunities to develop therapeutic targets.

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