In the last decade, a number of regulatory proteins have been shown to be important in the development and function of the pituitary gland. These transcription factors act at different stages of development to trigger the expression of specific genes that regulate the development of specific cell lineages, as well as the expression of hormone genes. Indeed, over the last year, several interesting articles in this challenging new area have been extremely helpful for understanding pituitary gland genetics and pathology, as well as the physiology of anterior pituitary hormonal regulation. Other selections should have important clinical implications for practicing physicians. The resulting summary will hopefully provide valuable help for updating busy pediatric endocrinologists on the most interesting and relevant work recently published in the field of pituitary studies and will furnish insights into future directions.

**Mechanism of the year**

**PROP-1 mutations: transition from hyperplasia to hypoplasia**

**Role of PROP-1 in pituitary gland growth**

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**Background:** The PROP-1 gene is a tissue-specific, paired-like, homeodomain transcription factor expressed early in the anterior pituitary. The Prop-1 gene plays an essential role in the evolution of pituitary cells secreting GH, PRL, TSH and gonadotropins, as shown by hormone deficiencies in subjects with PROP-1 mutations. ACTH deficiency seems to be more common than was formerly thought. Pituitary morphology in patients carrying PROP-1 mutation varies considerably between small, normal and up to an extremely enlarged pituitary gland size, with no abnormalities among pituitary stalk and posterior pituitary. Spontaneous mutant Ames dwarf mice, however, display pituitary hypoplasia. The mechanism whereby PROP-1 regulates anterior pituitary growth from pituitary hyperplasia to hypoplasia is still largely unclear.

**Methods:** Longitudinal studies in normal and Prop-1-deficient generated mice were carried out from early embryogenesis to adulthood. The volume of Rathke’s pouch and its derivatives, the position and number of dividing cells and the rate of apoptosis and cell migration were evaluated.

**Results:** Prop-1 deficiency results in early abnormal expansion of both Rathke’s pouch and of the lumen with late pituitary dysmorphology and severe hypoplasia. Volumetric analysis by three-dimensional reconstruction confirms pituitary growth pattern with tenfold pituitary volume reduction after birth. The volumetric measurements suggest that proliferating cells progressively fail to populate the anterior pituitary, while pulse chase labeling shows impairment of the migration pattern of progenitors from the periluminal region to the anterior lobe. After birth, mutant pituitaries displayed increased apoptosis.

**Conclusion:** Mutations in the transcription factor Prop-1 causes dysmorphic pituitary primordium, apparent Rathke’s pouch overgrowth and profound adult pituitary hypoplasia. The role of Prop-1 in pituitary gland development and growth is to promote the migration of progenitor cells from Rathke’s pouch into the anterior lobe, suggesting that pituitary hypoplasia in humans with PROP-1 defect could be due to trapped progenitor cells, while subsequent degeneration could be due to the apoptosis of undifferentiated cells.

Small anterior pituitary size is the most frequently observed pituitary feature in both mice and humans carrying PROP-1 mutations. One aspect of the mouse Prop-1-deficient phenotype that
remains unexplained is the profound dysmorphology of the dorsal aspect of Rathke’s pouch which appears overgrown and dysmorphic. Indeed, enlarged anterior pituitary with progression from a large and full sella turcica to suprasellar extension of a pituitary mass, followed by areas of cystic change, loss of contrast enhancement of the mass, and eventual regression to large empty sella has been described in subjects with PROP-1 mutations. The phenomenon of pituitary hyperplasia followed by a shrinkage of the pituitary gland has not been observed in Ames mice and it is still puzzling in humans. Several hypotheses have been put forth, including an abnormal proliferation of pituitary undifferentiated cells leading to a ‘pseudotumor’ mass. The mass may outgrow its vascular supply or may exert pressure on its own, feeding vessels leading to a partially empty sella and the sequence of events could be suggestive of apoplexy. Recently, it has been shown that patients with anterior pituitary enlargement can have spontaneous regression of the mass lesion that seems to originate from the intermediate lobe [1], providing information that may be helpful in clarifying the role of PROP-1 in the repression of other early pituitary transcription factors. Indeed, this study by the Sally Camper group provides basic information about how the pituitary gland forms and demonstrates a role of Prop-1 in progenitor migration from Rathke’s pouch into the developing anterior lobe. In addition, the study provides insight into our understanding of the mechanism of PROP-1 action and gives an explanation for the intriguing transition from pituitary hyperplasia to hypoplasia in humans with such a mutation. With loss-of-function, progenitors are trapped and cause a hyperplastic overgrowth; then they can undergo apoptosis and disappear. Moreover, this study provides a model for other pituitary endocrine diseases associating pituitary mass and pituitary dysfunction such as craniopharyngioma.

### Concepts revisited

**PROP-1 mutations cause progressive deterioration of anterior pituitary function including adrenal insufficiency: a longitudinal analysis**


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J Clin Endocrinol Metab 2004;89:5256–5265

**Background:** In humans, the clinical picture and hormone phenotypes of PROP-1 mutations partially resemble those of Pit-1 with low basal and stimulated GH, TSH, PRL and FSH/LH. The clinical phenotype varies considerably, especially according to the time of onset and the severity of the pituitary-derived hormone deficiencies. ACTH deficiency is a striking and unexpected associated feature that is not linked to a given mutation and has been reported in as many as one-third of these patients. Longitudinal data on the prevalence of adrenal insufficiency and the temporal pattern of anterior pituitary failure are still not available.

**Methods:** Forty-six patients with combined pituitary hormone deficiency were selected from 350 patients with GHD according to the following criteria: severe GHD, at least one additional pituitary hormone deficiency with or without abnormal pituitary morphology at MRI. The analyses of the Prop-1 gene and endocrine function testing were performed in all patients. The pituitary-thyroid-adrenal-gonad axis was evaluated by using dynamic stimulation tests.

**Results:** Homozygous or compound heterozygous mutations were identified in 9 patients (19.6%) who were diagnosed at a mean age of 4.9 years and followed for a mean of 15.7 years. All but 2 patients with enlarged anterior pituitary gland exhibited anterior pituitary hypoplasia. All patients displayed a decrease in GH response to classical pharmacological stimulation tests, as well as after GHRH. A decrease in TSH and PRL, as well as in FSH and LH responses, were recorded after TRH and GnRH, respectively. Basal morning cortisol and cortisol response after CRH or after ITT declined to an abnormal value in all patients, leading to treatment with hydrocortisone before the age of 20 years in 6 patients.

**Conclusion:** Patients with Prop-1 mutations show a progressive deterioration of anterior pituitary function that includes GH, TSH, PRL and FSH/LH defects. Unlike the mouse model, adrenal insufficiency is a common feature of Prop-1 deficiency in human beings.
Prop-1 is one of the transcription factors involved in pituitary development through a progressive reduction of Hesx-1 repressor activity. Its expression appears early in embryonic development and is crucial for the differentiation and function of somatotrophs, thyrotrophs, gonadotrophs and lactotrophs. But so far it was not implicated in the generation of corticotrophs. Moreover, failure of corticotroph function is not found in either in vitro or animal models and, unlike the Ames dwarf mice, human cross-sectional studies show that approximately one-third of patients with PROP-1 defect have adrenal insufficiency. The results of this study represent a further contribution to the management of patients with the most common form of genetically determined MPHD, as well as to the understanding of the role of PROP-1, not only in the embryonic differentiation process but also in pituitary cell maintenance and survival of corticotroph cells. Although the pathophysiology of ACTH deficiency remains to be clarified, one can argue from the reported figures of this study that several cases might have had ACTH deficiency before the start of GH treatment. The low GH concentrations reported in this study may, in fact, mask a subclinical condition of central hypoadrenalism, likely brought about by the enhancement of the conversion of inactive cortisone to active cortisol through the modulation of 11β-hydroxysteroid dehydrogenase activity. It may be premature to redraw our pituitary ontogenesis schemes and move PROP-1 into the pre-corticotroph stem cell.

Augmentation of growth hormone secretion after testosterone treatment in boys with constitutional delay of growth and adolescence: evidence against an increase in hypothalamic secretion of growth hormone-releasing hormone

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J Clin Endocrinol Metab 2004;89:3326–3331

Background: Puberty is associated with increased GH secretion and acceleration of linear growth. The augmentation of GH secretion involves increased amplitude, but not frequency, of pulse, and increased GH response to some secretagogues. The neuroendocrine mechanisms underlying the pubertal increase of GH secretion in boys are not completely understood, although it is known that they are mediated by aromatization of testosterone to estradiol. An increased hypothalamic release of GHRH has been hypothesized, but never proven.

Methods: The hypothesis that GHRH mediates the pubertal increase of GH secretion was tested in 6 early-pubertal boys with constitutional delay of growth using a constant infusion of a GHRH antagonist. Blood samples were obtained every 15 min for 24 h during the overnight infusion of normal saline and again during the overnight infusion of the GHRH antagonist (0.33 μg/kg/h). Subjects were then treated with transdermal testosterone (5-mg patch) for 12 h nightly and were studied again after 4 weeks.

Results: Mean 24 h GH area under the curve during testosterone increased by 115.7%. Mean pulse amplitude (cluster analysis) increased by 112% while pulse frequency was unaffected. Before testosterone treatment, the infusion of GHRH antagonist suppressed nocturnal GH secretion in all but 1 subject. During testosterone treatment, nocturnal GH secretion during the infusion of GHRH antagonist was suppressed in all but 1 subject. In the remaining 5 subjects, GH area under the curve was suppressed by 13.6–68.3% after T. In all 6 subjects, mean GH area under the curve was suppressed by 29.1 ± 9.5% before T and by 29.4 ± 11.2 after T (not significant). T treatment had no effect on pituitary response to exogenous GHRH or to 24 h Ghrelin concentrations.

Conclusions: The increased GH secretion during puberty was not apparently due to enhanced somatotrope sensitivity to GHRH stimulation. This study also showed that an increased release of endogenous GHRH does not mediate the pubertal augmentation of GH secretion in a semiquantification model of hypothalamic GHRH secretion in vivo in humans.

Spontaneous puberty in both boys and girls is characterized by increased GH secretion. The response of GH to several stimuli is increased in puberty, or after administration of testosterone or estrogens. Sex steroid priming is widely used to test pituitary function before the onset of the growth spurt, when, without priming, pharmacological and physiological tests may yield subnormal responses. Spontaneous GH secretion also progressively increases with puberty, a phenomenon mediated by the
A mouse with targeted ablation of the growth hormone-releasing hormone gene: a new model of isolated growth hormone deficiency
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Endocrinology 2004;145:4134–4143

Background: GH secretion is regulated by the combined and opposing action of hypothalamic GH-releasing hormone (GHRH) and somatostatin (SRIH), which respectively stimulate and inhibit its release from the pituitary. The release of these two neurohormones is, in turn, regulated by a complex network of neurotransmitters and neuropeptides. The importance of GHRH in regulating the synthesis and secretion of GH is demonstrated by the evidence that mutations in the GHRH receptor (GHRH-R) cause isolated GH deficiency (IGHD) in humans and mice (little mouse, lit). Pituitary hypoplasia owing to a deficiency of somatotroph cells is present in humans and lit. mice with GHRH-R gene mutations.

Methods: To determine the consequences of a generalized lack of GHRH, a mouse with targeted disruption of the GHRH gene was created (GHRHKO) by substituting a portion of the gene that encodes for the initial 14 amino acids of the 1–42 GHRH with a neomycin resistance cassette.

Results: The heterozygous GHRHKO male and female mice in the study had normal fertility. The adult −/− mice at autopsy showed no anatomic abnormalities of the internal organs. The −/− males had normal copulatory behavior and fertility. At 2 weeks of age, the −/− mice appeared slightly smaller than their littermates. By week 8 the weight of the −/− mice had reduced to 55–60% of the +/+ mice. The length of the −/− mice was also significantly reduced compared to the +/+ mice. The −/− animals had an evident reduction in pituitary size, GH mRNA concentration and IGF-I levels.

Conclusions: This is the first clean animal model of complete GHRH deficiency. The phenotype of the GHRHKO mice is similar to that of the lit/lit animals, indicating that the main function of GHRH is to stimulate GH secretion and that its function is mostly mediated by the GHRH-R expressed in the pituitary. This mouse model demonstrates that generalized ablation of the GHRH gene causes GH-dependent growth retardation. It will be also useful for studying the effects of different compounds on GH secretion in animals with intact somatotroph cells and intact GHRH-R.

Partial reversibility of growth hormone (GH) deficiency in the GH-releasing hormone (GHRH) knockout mouse by postnatal treatment with a GHRH analog
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Endocrinology 2005;146:1506–1513

Background: The same group has demonstrated that targeted ablation of the GHRH gene causes IGHD and pituitary hypoplasia in mice. It is not known whether exposure to endogenous GHRH during intrauterine growth is necessary for postnatal GH secretion or whether GHD due to congenital lack of GHRH activity could be reversed by postnatal treatment with GHRH.
Isolated GH deficiency (IGHD) can be due to abnormalities in the secretion or action of endogenous GHRH. Most children with IGHD grow when treated with GHRH, indicating normal functioning of somatotropes. Although genetic defects in the GHRH receptor and in GH genes have been identified, mutations in the GHRH genes have not yet been identified. One possible explanation is that a lack of GHRH has no ill effect due to redundant control mechanisms. Alternatively, it is possible that GHRH has other functions and that a lack of GHRH may cause a different phenotype than the one observed in GHRH-R mutations or be lethal for the embryo. Salvatori and co-workers have carried out two elegant and useful studies; in the first one, they created a GHRHKO mouse and showed that the phenotype is strikingly similar to that of the lit/lit mouse. In the second paper, joining forces with A.V. Schally, Nobel Laureate for discovering the first hypothalamic hormones, they showed that the pituitary of the GHRHKO mouse retains the ability to respond to exogenous GHRH with an increase in pituitary size and in GH synthesis. These studies add a new model for studying GHRH function and could possibly motivate new research in selected children with IGHD of hypothalamic origin. We will not be surprised if such an analog would develop into a growth-promoting pharmaceutical.
Di Chiro formula: \( V = \frac{1}{2} \text{length} \times \text{height} \times \text{width} \) which tends to underestimate or, alternatively, \( V = \text{area} \times \text{width} \), which tends to overestimate pituitary size. Changes with age in pituitary shape and size appear mainly due to changes in gland height. Pituitary height, in fact, is used as an indicating parameter for anterior pituitary size, though there is the risk of underestimating the size of a pituitary with a concave superior margin or overestimating one with a convex surface. The overall information based on three-dimensional pituitary volume provided by this study is important. However, the weak correlation between pituitary height and directly measured pituitary volume and between estimated pituitary calculation and measured pituitary volume make the simple evaluation of pituitary height unreliable. This technique cannot be used in children over 10 years of age or in adolescents. The relative discrepancy between the results of this study and two earlier reports [2, 3], as well as the absence of inter-observer evaluation, render its results incomplete; therefore further studies are required.

**Important for clinical practice**

**Prevalence of adrenocorticotropic deficiency in children with idiopathic growth hormone deficiency**

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**Background:** Approximately one-third of children with idiopathic growth hormone deficiency (IGHD) also suffer from other anterior pituitary hormone deficiencies. Between 6 and 11% are unable to mount an appropriate ACTH/cortisol response to stress. Thus, identification of patients with subclinical adrenal insufficiency is crucial for avoiding possible life-threatening consequences.

**Methods:** The electronic medical records system of a children’s hospital was used to identify all GHD-affected patients under 18 years of age. TSH and ACTH deficiency were defined as present if the patient was prescribed replacement hormone therapy. The medical records of 236 GHD subjects were reviewed, and the results of their MRI scans were recorded.

**Results:** Of the 236 subjects studied, 21 (9%) had TSH deficiency. Ninety subjects had undergone HPA testing with overnight metyrapone in the majority of cases followed by ACTH stimulation test and by single morning cortisol measurement. Insulin tolerance test (ITT) was seldom used. Nine subjects had ACTH deficiency and all of them were also TSH-deficient. Eight of the 9 ACTH-deficient subjects had a midline abnormality on MRI, either an ectopic posterior pituitary or an interrupted stalk.

**Conclusions:** This study indicates that ACTH deficiency is rarely found in patients with normal MRI and normal TSH. The authors suggest that children with IGHD, normal thyroid function and no gross abnormalities at MRI do not need HPA testing.

A substantial number of patients with IGHD may have additional anterior pituitary hormone deficits and be at risk of developing complete or partial ACTH deficiency. Among adult subjects with childhood onset GHD, 44% developed asymptomatic adrenal insufficiency. In this study, Walvoord et al. reported that all but 1 patient with GHD and additional ACTH deficiency had an ectopic posterior pituitary at MRI. However, although clinically asymptomatic, the hypothalamic-pituitary-adrenal axis (HPA) of these patients cannot appropriately respond to stressful stimuli with potential life-threatening consequences. Thus, evaluation of the integrity of the HPA is of fundamental importance in patients with GHD [4]. Although the diagnosis of overt adrenal failure is generally straightforward, identification of those asymptomatic patients with subtle dysfunction of the HPA axis is still a diagnostic challenge. The HPA axis response to insulin hypoglycemia (ITT) is still considered the gold standard in the evaluation of suspected adrenal insufficiency, even though its validity has recently been questioned. Furthermore, ITT is contraindicated in infants, and in patients with cardiovascular disease or a history of seizures. Patients with multiple pituitary hormone deficiencies experience severe hypoglycemia during ITT,
and occasional deaths in children have been reported with the use of such a test. Therefore, alternative tests to evaluate the HPA have been proposed such as glucagon, metyrapone, standard and low ACTH and corticotropin-releasing hormone (CRH) testing. None of these tests, however, is guaranteed to be completely reliable for establishing or excluding the presence of secondary or tertiary adrenal insufficiency unless local cut-off values are correctly established.

The results of this study have important implications in the clinical setting. They indicate, in fact, that virtually no patients with TSH sufficiency and normal MRI of the hypothalamic-pituitary area had ACTH deficiency. These findings are helpful in order to reduce the need for HPA testing, given its inconvenience, discomfort and cost.

Do all patients with childhood-onset growth hormone deficiency (GHD) and ectopic neurohypophysis have persistent GHD in adulthood?

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Background: It has been suggested that GHD of childhood-onset associated with congenital structural hypothalamic-pituitary abnormalities does not require further investigation of GH status after adult height achievement as compared to patients with isolated GHD and normal or small pituitary gland. The concept of anterior pituitary hypoplasia, posterior pituitary and pituitary stalk agenesis as markers of permanent GHD in adult life remains to be confirmed.

Methods: Eighteen subjects with childhood-onset GHD treated with rhGH for a mean of 9.9 years were re-evaluated for GH secretion at a mean age of 17.7 years; 8 had isolated GHD and 8 had MPHD. Growth hormone secretion was obtained after combined arginine insulin (n = 15) or propranolol glucagon (n = 3) stimulation test. The MRI of the hypothalamo-pituitary region was carried out in all patients at the time of diagnosis of GHD, as well as at the re-assessment of GH status in 12 of them.

Results: Growth hormone response was found to be <5 µg/l in 11 subjects (61%), between 5 and 10 µg/l in 3 patients (17%), and >10 µg/l in 4 subjects (22%). All of the patients in the study (except 1) who showed a GH response >5 µg/l had isolated GHD; the other patients (except 1) who showed a GH response <5 µg/l had MPHD. None of those with GH response >5 µg/l had complete pituitary stalk agenesis, as compared to those with GH response <5 µg/l. Posterior pituitary ectopia at the level of the median eminence mainly characterizes those with the lower GH-response group as compared to the others who showed posterior pituitary ectopia at the level of the proximal pituitary stalk.

Conclusion: Patients with childhood-onset and severe GHD associated with MPHD together with posterior pituitary gland at the level of median eminence have permanent GHD in adult life, whereas those with isolated GHD and partial pituitary stalk agenesis with posterior pituitary confined to the proximal part of pituitary stalk might have normal GH responses after GH-treatment withdrawal.

This study further contributes to our understanding of the natural history of idiopathic GHD of childhood-onset presenting with congenital structural hypothalamic-pituitary abnormalities. It confirms that the picture of severe GHD patients, defined as those with GH response <5 µg/l and the triad of anterior pituitary hypoplasia, pituitary stalk agenesis and posterior pituitary ectopia (EPP) at the level of the median eminence, are clearly candidates for permanent GHD in adult life [5], while those with less severe MRI features have an uncertain diagnosis or a likelihood of normal GH response after stimulation tests. These findings have important clinical implications in the diagnosis and prognosis of GHD after adult height achievement. Recent data, however, clearly show that when the criterion of a peak GH value of <3 or <5 µg/l after ITT is applied, several misdiagnosed GHD subjects would be wrongly excluded from a potentially beneficial continuation of rhGH replacement treatment [6]. On the other hand, the diagnostic cut-off value of peak GH that should be adopted in young adults after combined arginine insulin or propranolol glucagon (used by the authors) has yet to be established; the role of sex hormones following the onset of puberty should not be underestimated. Although the natural history of EPP is still unclear (ranging from untreated giant panhypopituitarism [7] to ‘apparently’ normal GH response), we believe that EPP associated with partial or complete pituitary stalk agenesis should not be considered a ‘normal variant’. In some young adults with childhood-onset
hypopituitarism, a strongly suspected diagnosis of permanent GHD might be investigated more accurately by means of an integrated analysis that includes clinical history, the presence of additional hormone deficits, serum IGF-I concentrations, MRI findings of structural hypothalamic-pituitary abnormalities, and the monitoring of GH-dependent endpoints, rather than exclusively by a GH cut-off point after stimulation test. The essential metabolic markers which are indicated in the diagnosis of adult GHD still need to have their accuracy confirmed in the diagnosis of young adults with childhood GHD.

**Congenital isolated adrenocorticotropic deficiency: an underestimated cause of neonatal death, explained by TPIT gene mutations**


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**J Clin Endocrinol Metab 2005;90:1323–1331**

**Background:** Transcription factors controlling early events of pituitary organogenesis have been implicated in combined or isolated pituitary hormone deficiency. TPIT is a cell-restricted transcription factor and is essential for cell-specific transcription of the POMC gene. Mutations of the TPIT gene have been found in rare cases of ACTH deficiency.

**Methods:** Sequence analysis of the TPIT gene was performed in 27 patients from 21 unrelated families affected by isolated ACTH deficiency.

**Results:** TPIT gene mutations were identified in 17 patients. The remaining 10 patients had no gene anomalies in coding sequences. The parents of the patients carrying TPIT gene mutations were consanguineous in 5 out of 13 families. Eleven of the 17 affected patients also had a neonatal history of prolonged cholestatic jaundice that disappeared after glucocorticoid replacement. Ten different mutations were identified within the coding regions of the TPIT gene. Analysis of the parents’ DNA indicated that they were all unaffected heterozygous carriers. In five families, a neonatal death was recorded.

**Conclusions:** In this large series of patients with congenital ACTH deficiency, a mutation of the TPIT gene was found in a majority of cases. Identification of TPIT gene mutations permits prenatal diagnosis for at-risk families in order to start early glucocorticoid replacement therapy.

TPIT is a T-box transcription factor which is important for terminal differentiation of pituitary POMC-producing cells. Human and mouse mutations of TPIT genes had previously been shown to cause a neonatal-onset form of isolated ACTH deficiency (IAD). This study showed that a mutation in the TPIT gene was the cause of disease in a large series of patients with IAD. All of the patients appeared to be homozygous or compound heterozygous for TPIT mutations and their unaffected parents were heterozygous carriers, confirming recessive inheritance. The patients in the study revealed a highly homogeneous clinical presentation. These findings have major implications for genetic counseling, prenatal diagnosis, and early verification and treatment of affected newborns.

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**New mechanisms**

**Alu-element insertion in the homeodomain of HESX1 and aplasia of the anterior pituitary**


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**Hum Mutat 2005;25:503**

**Background:** Pituitary gland aplasia is a rare life-threatening disease with severe clinical phenotype in neonatal age subjects which includes hypoglycemic seizures, adrenal and thyroid insufficiency, as well
as respiratory distress leading to high death rate. None of the identified genes involved in pituitary organogenesis have so far elucidated the molecular basis of anterior pituitary aplasia.

**Methods:** A proband, the fourth child of consanguineous parents, had the clinical and endocrine features of panhypopituitarism, right eye blindness with microphthalmia, microcornea, and iris and chorioretinal coloboma. MRI showed hypoplastic sella turcica, no evidence of anterior pituitary gland tissue, and posterior pituitary hyperintensity at the distal end of the pituitary stalk. A younger brother with similar endocrine and pituitary phenotypes had died from aortic coarctation 18 h after birth. HESX-1 gene was amplified and the 4 exons were sequenced. Primers were used to amplify the region of Alu-element insertion in exon 3.

**Results:** The proband carries the HESX-1 mutation in the homozygous state, an Alu insertion in exon 3, a sequence that encodes the major part of the homeodomain. The Alu-containing HESX-1 allele generates a major transcript that lacks this exon (proband) and a minor one in which exons 2 and 3 skipped (mother), predicting severely truncated proteins.

**Conclusion:** Alu-element insertion in the homeodomain of HESX-1 causes panhypopituitarism, anterior pituitary aplasia, normal posterior pituitary location and optic nerve coloboma. This data strengthens the heterogeneity of HESX-1 expression in diseases involving pituitary gland and optic nerve development.

This study describes the first molecular abnormality identified so far in human pituitary aplasia involving the transcription factor HESX-1. Several pituitary-specific transcription factors play a role in the determination of pituitary cell lineages and in pituitary development, as shown in knockout and mutant animals studies. Mutations in many of these transcription factors, including PIT-1, PROP-1, LHX-3, LHX-4, GLI-2 and SOX-3, have been identified so far in patients with hypopituitarism and different pituitary phenotypes at MRI. In particular, HESX-1 is necessary for normal development of the forebrain, eyes, olfactory placodes and anterior pituitary gland as shown in null mutants and in humans. Eight mutations (including the mutation reported at the Endocrine Society Meeting, 2005) of the HESX-1 gene have been reported in the familial form of septo-optic dysplasia and in some other hypopituitarism-related conditions. The pituitary phenotype in HESX-1 mutations has been reported to be associated with: agenesis of the corpus callosum, hypoplasia of the optic nerves, pituitary hypoplasia and ectopic posterior pituitary. In other cases, MR imaging examination has evidenced unilateral hypoplasia of the optic nerve associated with normal or hypoplastic pituitary gland in patients with isolated GH deficits or with panhypopituitarism. This new HESX-1 mutation combining aplasia of the anterior pituitary and coloboma suggests that the pituitary phenotype in HESX-1 mutations is rather complex and reflects the heterogeneity of multiple conditions with different interacting pathways affecting forebrain/midbrain development.

**Over- and underdosage of SOX-3 is associated with infundibular hypoplasia and hypopituitarism**


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**Background:** Recent studies implicate SOX-3, a single exon gene closely related to SRY, in the etiology of X-linked hypopituitarism in both humans and mice. The phenotype of SOX-3 mutant mice is variable and complex, with abnormalities throughout the hypothalamic-pituitary-gonadal axis [8]. Indeed, in humans, mutations of SOX-3 and duplications at Xq26–27 are implicated in a syndrome of X-linked hypopituitarism and mental retardation [9, 10]. The dosage of SOX-3 could be critical for pituitary development and function.

**Methods:** Seventy-six male probands were screened for mutations within SOX-3, and 19 were tested for a duplication by interphase FISH analysis. Clinical and endocrine data and MRI of the brain and pituitary gland were collected for all patients. Polymorphic microsatellite markers mapping near SOX-3 and elsewhere on the X chromosome were amplified.
Results: A submicroscopic duplication at Xq27.1 containing SOX-3 and two other transcripts of unknown function was found in 2 siblings with variable endocrine phenotype and pituitary features of anterior pituitary hypoplasia, posterior pituitary ectopia, absent infundibulum and abnormalities of the corpus callosum. Moreover, a novel polyalanine expansion from 15 to 22 alanine residues within SOX-3 were identified in 3 brothers with panhypopituitarism with an MRI picture similar to that described in the above patients and a polymorphism (A431) in SOX-3 in a child with GH and thyroid hormone deficiency and hypoplastic corpus callosum was also identified. None of the subjects showed evidence of mental retardation.

Conclusion: Over- and underdosage of SOX-3 are associated with variable endocrine phenotype, i.e. isolated GHD, combined pituitary hormone deficiency and panhypopituitarism, as well as with peculiar pituitary features and CNS abnormalities in the absence of mental retardation.

This study highlights the role of SOX-3 in the human brain and in hypothalamic-pituitary organogenesis and function. It provides valuable information for understanding the puzzling network of transcription factors involved in pituitary organogenesis. Both SOX-3 over- and underdosage cause clinical and endocrine hypopituitarism-related conditions associated with posterior pituitary ectopia, anterior pituitary hypoplasia and abnormality of both the infundibulum and the corpus callosum. This suggests that SOX-3 is involved in the development of midline forebrain structures. Although the full contribution of genetic background to the variability of the SOX-3 mutant (duplication, expansion, polymorphism) or phenotype has yet to be explored, there is a good chance that SOX-3 mutations in humans may account not only for familial forms of hypopituitarism, but also for sporadic conditions of GH deficiency. Indeed, as in HESX-1 and LHX-4 mutations, both associated with a variable MRI picture including posterior pituitary ectopia, hypothalamic-pituitary development appears to be critically dependent upon SOX-3. This implies that selection of some ‘idiopathic’ GHD patients for molecular analysis may be worthwhile. The absence of mental retardation suggests that SOX-3 is the candidate gene most likely implicated in male hypopituitarism, in agreement with the reported male-to-female preponderance.

Pitx genes are required for cell survival and Lhx-3 activation

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Background: Two members of the Pitx family of homeobox-containing transcription factors, Pitx-1 and Pitx-2, have been implicated in several aspects of pituitary development and transcriptional regulation. Hormone genes and lineage-specific transcription factors are among the downstream targets of the Pitx genes in the pituitary. On the other hand, antisense knockdown of Pitx-1 in cell culture leads to the extinction of Lhx-3, another transcription factor involved in pituitary development. Little is known about the sensitivity of these target genes to Pitx dosage or the functional overlap the two Pitx genes may have in their activation.

Methods: Pitx-2 null mice were generated by gene targeting and overexpression of Pitx-2 in pituitary cells by transgene construction. Embryos were fixed and samples were sectioned and prepared for immunohistochemistry using several antibodies to detect transcription factors or signaling molecules.

Results: Loss of Pitx-2 leads to increased cell death during early development. The location of apoptotic cells in the pituitary was shifted dorsally as compared to the wild type where apoptosis was confined to the base of Rathke’s pouch. This led to severe pituitary hypoplasia. Transgenic overexpression of the Pitx-2 showed a marked increase in the gonadotropes only, with no evidence of a change in other cell populations. Indeed, Pitx-1 and Pitx-2 were found to be expressed throughout the anterior lobe in both the embryonic and the adult pituitary. The mice lacking Pitx-1 and Pitx-2 failed Lhx-3 expression.

Conclusion: Lack of Pitx-2 and double knockouts of Pitx-1 and Pitx-2 are associated with pituitary hypoplasia in mice. The absolute concentration of Pitx-2 is important for normal pituitary cell expansion, suggesting that the Pitx family has a vital role in pituitary development and in maintenance of pituitary function.
Pitx-1 and Pitx-2, two members of the Pitx family of homeobox-containing transcription factors, were knocked out in mice, and both affected the development of many organs. Mice completely lacking Pitx-1 had severe hind limb defects, cleft palate, mildly affected pituitary gland and died after birth. While Pitx-1 is not associated with any known human disease, mutation in a single allele of Pitx-2 is associated with Rieger syndrome (defects in the eyes, teeth, umbilicus, and heart, as well as cases of isolated GHD defect) which is thought to be primarily a disease of haploinsufficiency. Indeed, the Rathke’s pouch of Pitx-2−/− mice failed to expand and develop an anterior lobe in contrast with the findings of a paucity of Pitx-2-positive somatotropes that cannot account for the report of isolated GHD in some Rieger patients. The discovery of the role of the Pitx family of transcription factors that act upstream of Lhx-3 represents a further step forward in the understanding of the complex signaling pathway involved in pituitary development and could be extremely helpful in the identification of different hypopituitarism-related conditions.

Mouse GnRH receptor gene expression is mediated by the LHX-3 homeodomain protein
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Background: GnRH receptor (GnRHR) function is essential for the function of the reproductive axis. GnRH receptor gene expression is regulated by a number of hormones and factors acting in the proximal promoter region of the gene. LHX-3, a member of the LIM homeodomain family, is essential for pituitary development and has been implicated in the regulation of a number of specific genes. This study examines the role of LHX-3 in the regulation of GnRHR gene function.

Methods: Basal expression of the GnRHR gene was studied in the gonadotrope-derived cell line, αT3-1, which endogenously expresses GnRHR, by using transient transfections, and luciferase and β-galactosidases assays.

Results: An ATTA element located at -298 relative to the transcriptional start site that is essential for basal expression of the GnRHR gene was identified. LHX-3 binds to the -298 ATTA site in vitro, as well as to the endogenous GnRHR promoter in vivo, and this binding activates the ATTA site in transient transfection assay.

Conclusions: This is the first report showing the role of LHX-3, a member of the LIM proteins family, in the regulation of GnRHR gene expression.

Several transcription factors participate in pituitary development and in regulation of transcription of specific pituitary genes. LHX-3 is a member of the LIM homeodomain family of transcription factors and is essential for normal pituitary development. Mutations in the LHX-3 genes cause combined pituitary hormones deficiency with rigid cervical spine. Normal reproductive function depends on the integrity of the hypothalamic-pituitary-gonadal axis, of which the GnRHR is a crucial player. This study shows that LHX-3 is one of the regulators of GnRHR gene expression, thus increasing our knowledge of the regulation of the hypothalamic-pituitary-gonadal axis. Since the expression of LHX-3 continues throughout adulthood, it is possible that its role is not confined to embryonic development, but rather extends into adult life. It is tempting to speculate that this transcription factor plays a role in maintaining normal reproductive function in adult life.
Loss of Gq/11 family G proteins in the nervous system causes pituitary somatotroph hypoplasia and dwarfism in mice

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Background: Heterodimeric G proteins of the Gq/11 family transduce signals from a variety of neurotransmitter and hormone receptors and have been implicated in various functions of the nervous system. The role of Gq/G11-mediated signaling in pre- and postnatal development, as well as in central nervous system function, is still unclear.

Methods: Mice lacking one to four alleles of the genes encoding for the α-subunits of the two main members of the Gq/11 family, gnaq and gna11 in neural and glial precursor cells were generated. Plasma IGF-1 and Ghrelin concentrations, as well as GH, TSH ACTH, thyroxine and corticosterone levels, were measured at 15 days postnatally. Immunohistochemical studies of brain and pituitary extracts were performed and food uptake was evaluated before and after Ghrelin injection in the mice arcuate nucleus.

Results: Null mice of gnaq and gna11 genes were morphologically normal at birth but they died shortly after delivery because of abnormal breathing. Mice with only one gna11 allele were severely growth retarded after day 5, had ataxia and died prematurely between third and sixth postnatal weeks because of failure to thrive. The size and weight of their pituitaries was reduced. Blood GH and IGF-1 levels were low, while the remaining hormones were spared. These conditions were due to a defect in postnatal cell proliferation related to GHRH defect. On the other hand, Ghrelin-induced GH release was inhibited through the GH secretagogue receptor (GHS-R). Exogenous administration of GHRH restored normal somatotroph proliferation.

Conclusions: Gq/11 signaling is required for normal hypothalamic function and pituitary cell proliferation. Anterior pituitary hypoplasia and abnormal eating behavior suggest that both defects involve impaired signaling via the GHS-R.

The Gq/11 family of heterodimeric G proteins mediates the cellular effects of a number of neurotransmitter receptors, and are involved in the signal transduction of several hypothalamic peptide hormone receptors including the TRH and the GnRH receptors. There is now increasing evidence that release of hypothalamic hormones is also controlled by Gq/11-coupled receptors. The kiss-1/GPR54 system is a recently reported modulator of reproduction function, and Kisspeptins have been implicated in the control of GnRH release via the Gq/11-coupled receptor GPR54 and Ghrelin regulates the production of GnRH via the GH secretagogue receptor (GHS-R). The results of this study show that a complete loss of Gq/G11-mediated signaling in the CNS is not associated with developmental abnormalities, but rather with a functional defect that leads to postnatal premature death. Moreover, the outcome in mice suggests that Gq/G11-mediated signaling is crucial for postnatal CNS function and survival. Specifically, mice carrying a single mutant gna11 allele showed ataxia, marked growth retardation, reduction of anterior pituitary size and cell numbers resulting in functional GH deficiency, reduction of food intake and failure to thrive. The impaired somatotroph proliferation, which was accompanied by a decrease in GHRH production, was reversible after GHRH administration and was revealed to be mediated through the GHS-R. The study’s results suggest that GHS-R is necessary for normal regulation of growth and energy homeostasis.

Ikaros integrates endocrine and immune system development

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Background: Several transcription factors are implicated in the process of pituitary development and expression of tissue-specific genes. Increasing evidence indicates that the endocrine and immune
systems are functionally integrated to coordinate stress response. Ikaros is a transcription factor originally described as involved in the regulation of genes expressed in lymphoid cells, and subsequently found to be expressed in the mouse pituitary. This study investigated the direct role of Ikaros in the development and function of the pituitary-adrenal-cortical system.

Methods: Northern and Western blotting and EMSA were employed to detect Ikaros in mouse corticomedelanotroph AtT20 cells. Transfection and co-transfection experiments were carried out to verify binding to the POMC promoter and regulation of gene expression. The pituitary gland of mice with disruption of the Ikaros gene was examined, as well as the hormonal and developmental profiles of Ikaros $-/-$ mice vs. heterozygous and wild-type animals. Lymphocyte reconstitution in Ikaros $-/-$ mice was performed by wild-type bone marrow reconstitution of the $-/-$ phenotype. The effect of glucocorticoid replacement on Ikaros null mice was investigated.

Results: Ikaros was expressed by pituitary corticomedelanotroph cells and the pituitary POMC genes were found to contain functional Ikaros binding sites. Ikaros bound to the POMC promoter and regulated gene expression, and its loss disrupted pituitary corticotroph cell development. Loss of Ikaros impaired pituitary-directed adrenocortical function, which was repairable by glucocorticoid treatment. Adrenocortical dysfunction in Ikaros null mice is not reversed by wild-type lymphocyte reconstitution.

Conclusion: This is the first study showing direct involvement of the Ikaros gene in the development and function of pituitary corticotropes. The identification of Ikaros as a factor involved in the regulation of the POMC-ACTH-adrenal axis provides new insights into the transcriptional mechanisms which interface the neuroendocrine and immune systems.

Ikaros proteins are zinc finger transcription factors involved in lymphopoietic cell differentiation and immune functions. Mutations of the Ikaros gene have been found in infants with acute lymphoblastic leukemia. This important study reports that the Ikaros gene is crucial in the development of the pituitary gland and in corticomedelanotroph function. In fact, Ikaros regulates POMC gene expression, which was almost undetectable in the Ikaros-deficient mice of the present study. Furthermore, the role of Ikaros in pituitary corticotroph development is independent of its function in the immune system. Ikaros-deficient mice die because of adrenocortical insufficiency and can be rescued by glucocorticoid replacement. As one of the previous articles in this chapter showed, most patients with isolated ACTH deficiency have TPIT mutations, and therefore analysis of the Ikaros gene may be helpful in diagnosing patients with central hypoadrenalism.

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New endocrine-related neurotransmitter

**Apelin, a potent diuretic neuropeptide counteracting vasopressin actions through inhibition of vasopressin neuron activity and vasopressin release**


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**Background:** Apelin is a bioactive peptide that acts on specific receptors expressed in rat hypothalamic nuclei involved in the control of body fluid homeostasis and neuroendocrine regulation. Apelin-immunoreactive neurons are abundant in the supraoptic (SON), paraventricular (PVN) and arcuate nuclei and are expressed by oxytocin (OXY) neurons. The role of apelin in modulating vasopressin (AVP) neuron activity and release has not yet been clarified.

**Methods:** The characterization of the predominant form of apelin and its distribution in various rat brain regions, and in the pituitary and pineal glands, as well as its plasma concentration, were analyzed. A study of the electrical activity of SON AVP neurons after intraventricular injection of apelin in lactating rats, and that of hypothalamic expression of apelin and its plasma concentration after water deprivation were performed. The central effects of apelin on systemic AVP release, diuresis, natriuresis and kaliuresis in conscious lactating mice was studied.

**Results:** The predominant molecular forms of endogenous brain, hypothalamic and plasma apelin were identified as apelin 13 and, to a lesser extent, apelin 17. In lactating rats, the SON and PVN...
magnocellular neurons showed the co-localization of both AVP and immunoreactive apelin. The electrical activity of AVP neurons after the injection of apelin 17 into the third ventricle showed a progressive and persistent inhibitory apelin-related effect. The water deprivation test resulted in an increase in hypothalamic apelin levels that was mirrored by decreased plasma apelin concentrations, suggesting a hypothalamic accumulation of the peptide under dehydration.

Conclusions: Apelin co-localizes with vasopressin in magnocellular neurons and inhibits the typical phasic firing pattern of these neurons resulting in decreased systemic AVP release and increased diuresis. The coexistence of the two peptides and their opposite biological effects and regulation highlight the crucial role played by apelin, through counteracting AVP actions, in the maintenance of body fluid homeostasis.

Following the Ghrelin story, here is another stomach-hypothalamus association. Apelin is a bioactive peptide recently isolated from bovine stomach extracts. Apelin-immunoreactive neurons are particularly abundant in the supraoptic (SON), paraventricular (PVN), and arcuate nuclei. Moreover, high densities of apelin nerve fibers and terminals have also been visualized in the SON, the PVN, the internal layer of the median eminence, and the posterior pituitary. Expression of apelin receptors has been found in magnocellular AVP neurons, suggesting that apelin might be involved in the regulation of AVP release and body fluid homeostasis. This hypothesis was supported by the study’s physiological experiments, which showed that intracerebroventricular injection of apelin inhibited basal or dehydration-induced release of AVP, as well as dehydration-induced water intake.

The results of this study represent further understanding of the physiology of water homeostasis. The pattern of apelin response to dehydration, with subsequent hypothalamic storage and reduction of plasma concentration, is the opposite of that of vasopressin, which is released under water deprivation and which results in hypothalamic depletion. This study demonstrates that apelin and vasopressin are regulated conversely in such a way so as to make AVP release possible and to sustain its antidiuretic action. Indeed, the role of apelin in water and electrolyte disorders including essential hyper- and hyponatremia should be elucidated. The stomach connection remains an enigma.

Reviews

Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up

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Background: Craniopharyngiomas account for 2–5% of all intracranial neoplasms and 5.6–13% of intracranial tumors in children. Despite their benign histological nature, their prognosis and outcome may be unfavorable due to the proximity of the tumor to vital structures and to the hypothalamic-pituitary area. This study reports the natural history of 121 patients with craniopharyngioma seen at the Departments of Endocrinology and Paediatrics in Oxford over a 40-year period.

Methods: The medical records of 121 patients (aged between 2.5 and 83 years at presentation) who presented with craniopharyngioma were studied. Imaging data at presentation were available for 107 patients (skull x-rays 5; pneumoencephalography 2; CT scanning 47; MRI 36; CT + MRI 16). Pituitary function was evaluated by means of provocative tests for GH (ITT, glucagon, clonidine) and ACTH (ITT, glucagon or short synacthen test), basal gonadotropin and sex steroid measurements, basal TSH and thyroid hormone measurements, and urine osmolarity. Patients were divided into four groups according to treatment: group A (n = 16) with gross total removal of the tumor mass; group B (n = 3) gross total removal + radiotherapy; group C (n = 51) partial removal; group D partial removal + radiotherapy (n = 33); group E (n = 6) cyst evacuation alone; group F (n = 3) cyst evacuation + radiotherapy. Follow-up imaging was performed at regular intervals. The mean follow-up period after presentation was 115 months for children and 96 months for adults. The mean follow-up period after therapeutic intervention was 108 months for children and 86 months for adults.
**Results:** The duration of symptoms before diagnosis ranged from 0.5 to 240 months. The most frequent symptoms at presentation were headaches (64%), visual field defects (55%) and decreased visual acuity (39%). Signs of increased intracranial pressure were recorded in a higher proportion of children than in adult subjects. The great majority of patients had pituitary hormone deficiencies. The frequency in children was 95% for GH, 77% for FSH/LH, 24% for ACTH, 25% for TSH, and 12% for vasopressin. The vast majority of craniopharyngiomas (94%) had an extrasellar extension, with 46% being predominantly cystic. All patients were surgically treated with a mortality rate of 1.8% after primary surgery. Total removal of the tumor with or without radiotherapy provided the best outcome. After a 10-year follow-up, 62% of subjects who had partial resection showed recurrence of the tumor, a figure that improved to 23% when surgery was followed by radiotherapy. No preoperative morphological criteria of the tumors were helpful in predicting the outcome. Pituitary function did not recover in any of the patients after treatment. Total removal of the tumor with or without radiotherapy provided the best outcome. After a 10-year follow-up, 62% of subjects who had partial resection showed recurrence of the tumor, a figure that improved to 23% when surgery was followed by radiotherapy. No preoperative morphological criteria of the tumors were helpful in predicting the outcome. Pituitary function did not recover in any of the patients after treatment. Total removal of the tumor with or without radiotherapy provided the best outcome. After a 10-year follow-up, 62% of subjects who had partial resection showed recurrence of the tumor, a figure that improved to 23% when surgery was followed by radiotherapy. No preoperative morphological criteria of the tumors were helpful in predicting the outcome. Pituitary function did not recover in any of the patients after treatment. Total removal of the tumor with or without radiotherapy provided the best outcome. After a 10-year follow-up, 62% of subjects who had partial resection showed recurrence of the tumor, a figure that improved to 23% when surgery was followed by radiotherapy. No preoperative morphological criteria of the tumors were helpful in predicting the outcome. Pituitary function did not recover in any of the patients after treatment. Total removal of the tumor with or without radiotherapy provided the best outcome. After a 10-year follow-up, 62% of subjects who had partial resection showed recurrence of the tumor, a figure that improved to 23% when surgery was followed by radiotherapy. No preoperative morphological criteria of the tumors were helpful in predicting the outcome. Pituitary function did not recover in any of the patients after treatment. Total removal of the tumor with or without radiotherapy provided the best outcome. After a 10-year follow-up, 62% of subjects who had partial resection showed recurrence of the tumor, a figure that improved to 23% when surgery was followed by radiotherapy. No preoperative morphological criteria of the tumors were helpful in predicting the outcome. Pituitary function did not recover in any of the patients after treatment. Total removal of the tumor with or without radiotherapy provided the best outcome. After a 10-year follow-up, 62% of subjects who had partial resection showed recurrence of the tumor, a figure that improved to 23% when surgery was followed by radiotherapy. No preoperative morphological criteria of the tumors were helpful in predicting the outcome. Pituitary function did not recover in any of the patients after treatment.

**Conclusions:** This long-term study confirms that craniopharyngiomas are often associated with substantial morbidity, although there has been an improvement in the last two decades. Establishing prognostic factors and the impact of new therapeutic approaches remain a primary goal.

Craniopharyngioma is the most common tumor affecting the hypothalamic-pituitary region, and accounts for approximately 10% of all childhood intracranial tumors. Although the histology is benign and the overall survival rate is high, hypothalamic-pituitary damage increases morbidity. In this review, the authors have presented an update on the management and long-term follow-up of craniopharyngioma. It is a must for pediatric endocrinologists who are involved in the management of pituitary tumors in clinical practice. It provides a comprehensive and updated overview on the therapeutic approaches and morbidity of a locally aggressive tumor, emphasizing that a high level of vigilance must be maintained over time in the patients. We are impressed by the well-known but little practiced benefit of cranial irradiation along with surgery. It may hurt the surgeon’s ego, but may prevent a substantial number of relapses.

**References**
