A 14-month-old boy was admitted to the Emergency Department because of two recent brief episodes of hypotonia and mental disconnection of 2-3 minute duration. He had been born by caesarean section at 41 weeks of gestation. Birth weight 3860 g, body length 51 cm. Neonatal hyperbilirubinemia (14.5 mg/dl) and apparent hypoglycemia have been reported. The mother reports similar episodes since 2 moth of age, mainly during the morning after prolonged fast, which were improved by feeding. Family history is unremarkable except for renal chronic insufficiency in his maternal grandmother.

At admission, the patient was alert, reactive, without neurological signs and hemodynamically compensated. Weight was 9520 g (SDS - 1.08), body length 73.4 cm (SDS - 1.24), anterior fontanel 1 x 1 cm, closed posterior fontanel. A smooth euthermic skin was present. Tanner’s stage 1, 3.5 x 1 cm phallus and two 2 ml scrotal testes were detected. Neurological development was normal for age.

Mental episodes were considered seizure equivalents. Blood glucose was 53 mg/dl (N: 60-110), sodium 138 meq/l (135-145), potassium 4.4 meq/l (3.5-5.5), pH 7.32, pCO2 35.9, bicarbonate 20.9, base excess -3.2, urea 42 mg/dl (10-40), Hemogram: Leukocytes 8650/mm3, with 67% lymphocytes, hemoglobin 10.8 g/dl, platelets 202,000/mm3. A preliminary diagnosis of hypoglycemic seizures was made.

Neurological examination and a brain computed axial tomography, as well as the electroencephalogram, was normal.

Comments.

Normal blood glucose levels are essential for brain metabolism which requires glucose as energy source. Brain glucose deficiency can produce severe brain damage. For a comprehensive diagnosis of hypoglucemia, it is necessary to understand the mechanisms that maintain blood glucose levels within a narrow margin, between 2.5 and 7.5 mmol/l (45-135 mg/dl), during food intake and fasting. In brief, after food intake, the body stores energy as hepatic and muscle glucogen and triglycerides in fat tissue. During fasting, the liver releases glucose and ketone bodies. Maintenance of normal blood glucose depends on:

1) normal functioning of enzymes involved in glyconeogenesis and glycogenolysis.
2) Adequate provision of endogenous substrates for gluconeogenesis (aminoacids, glycerol, lactate)
3) Adequate energy provision from beta-oxidation of fatty acids to generate glucose and ketone bodies. The latter are used as alternative substrates to glucose in peripheral tissues.

4) A normal endocrine system to integrate and modulate all these processes.

Based on the source of glucose homeostasis can be divided in 5 phases:

1) **Absorption.** Glucose provided by food ingestion elevates insulin levels and glucagon secretion is suppressed. Energy excess is stored as glycogen and lipids. Hypoglycemia in this phase is suggestive of hyperinsulism.

2) **Post-absorption or early fasting** (3-4 hours after eating). Insulin returns to basal levels and glucagons rises to activate hepatic glycogenolysis. Hypoglycemia in this phase is suggestive of a disorder in glucogenolysis (glycogenosis)

3) **Intermediate fasting phase.** (12-16 hours alter eating) Glycogeneogenesis takes over as the main glucose source. Hypoglycemia in this phase is suggestive of a defect in glycogenogenesis

4) **Prolonged fasting phase.** Hypoglycemia in this phase is suggestive of deficits in fatty acid metabolism (beta-oxidation)

5) **Hormonal phase.** GH and cortisol act as contra regulating factors avoiding fasting hypoglycemia.

In our patient, since hypoglycemic symptoms were observed after prolonged fasting, hyperinsulinism was unlikely [1]. In infancy fasting hypoglycemia, deficiency of contra regulatory hormones (ACTH-cortisol and GH) should be ruled out. Particularly, if other signs or symptoms, such as short stature, micropenis, cryptorchidism, midline defects, are present, pituitary deficiency should be discarded. Isolated or multiple pituitary deficiency symptomatology during the first years of life is mainly related to GH metabolic actions rather than growth promoting effects. Even though, an early deterioration of growth rather than weight is frequently detected as early as at 6-12 months of age [2]. In this patient, difficulties at delivery could have been related to fetal pituitary deficiency. Figure 1 depicts that body length was below genetic range. Diagnostic tests in these patients should be carried out during spontaneous or fasting-induced hypoglycaemia. Insulin, cortisol, GH levels and intermediate metabolites (lactic acid, ketone bodies and free fatty acids), as well as other pituitary hormones, are estimated for diagnostic orientations.

Serum hormone determinations were as follows: TSH 0,73 µUI/ml (Normal, 0.97-4.35), T4 4.2 µg/dl (6.7-14.5), free T4 0,51 ng/dl (0.89-1.93), T3 0,69 ng/ml (0.99-2.26), GH 0,78, Cortisol 7,9 µg/dl, Prolactin 22,3 ng/ml. Low serum T4 and free T4 along with an inappropriately low TSH suggest **Central Hypothyroidism**, therefore patient was put on 4 µg/Kg.day Levothyroxine. Moderate fast challenges were carried out to detect hypoglycemia. During an asymptomatic hypoglycemia serum GH was 1.1 ng/ml, serum insulin 1-3 µUI/ml, and Cortisol 8 µg/dl. Hormone values during hypoglycemia suggest **GH deficiency** but this diagnosis requires confirmation. In this patient, an arginine stimulation test had the following results of serum GH: basal 1.4, 30 min 2.1, 60 min 1.1, 90 min <0.05 and 120 min 1.8 ng/ml, supporting the diagnosis of GH deficiency. The interpretation of serum cortisol level was difficult because the boy was taking corticoids to treat laryngitis. Serum thyroid hormone levels under treatment were normal (TSH 1.88 µUI/ml, free T4 0.93 ng/dl, T4 8.8 µg/dl and T3 1.74 ng/ml).

**Comments.**

Hormone studies in this patient indicated the existence of at least TSH, ACTH and GH deficiencies. Normal serum prolactin concentrations suggest normal lactotrophic function. At his age, gonadotropic function is difficult to evaluate.
Gh has a central role in maintenance of glucose homeostasis stimulating free fatty acid and ketone body utilization. It also induces insulin resistance protecting against hypoglycaemia. During fasting, GH increases favouring anabolism along with decreases in catabolic hormones (glucagon, epinephrine and cortisol), while insulin and IGF1 decrease[3]. Children with GH and/or cortisol deficiency have decrease liver production of glucose, insulin levels are inhibited and ketonemia increases. Incidentally, it is important to remember that hyperketonemia is not observed in neonates and infants.

Glucocorticoid treatment was discontinued and rhGH treatment was started at a dose of 0.5 IU/Kg.week, but hypoglycemia did not subside. Indeed, 4 days after the onset of rhGH, blood glucose was 26 mg/dl and cortisol 9.1 µg/dl. Cortisol level was considered relatively insufficient for such a low glycemic value. Therefore, the patient initiated oral hydrocortisone treatment (15.9 mg/m2.day.

Nuclear Magnetic Resonance imaging of the pituitary showed a hypoplastic pituitary gland with absent pituitary stalk (Figure 1).

Comments.
The diagnostic value of cortisol and GH levels during spontaneous hypoglycemia has been recently questioned. Kelly et al. [4] showed that low serum cortisol (<18 µg/dl) and GH (<10 ng/ml) during hypoglycaemia is not specific to diagnose pituitary deficiency. The low-ACTH stimulation test is better test for adrenal insufficiency but it not always available. Recently, di Iorgi et al. [5] proposed a glucagon diagnostic test as an accurate diagnostic test to evaluate adrenal function without side effects (as the insulin hypoglycaemia test) in young children at risk for adrenal insufficiency. Glucagon is administered im at a 30 µg/Kg dose and serum cortisol is determined at times 0-180 minutes. The cutoff was established at 14.6 µg/dl.
In this patient, low serum cortisol during hypoglycaemia which did not improve under rhGH treatment suggests associated ACTH-cortisol insufficiency. Moreover, MNR imaging defects, such as anterior pituitary hypoplasia and absence of pituitary stalk are frequently associated to multiple pituitary deficiency [6].

Thirteen days after onset of rhGH and 9 days after hydrocortisone two additional episodes of hypoglycemia were detected after at least 8 hour fasting. Therefore, recommendation of frequent feeding was reinforced, and rhGH dose was increased to 0.85 IU/Kg.week. The boy was discharged after 44 days in the Hospital with the diagnosis of panhypopituitarism, receiving hydrocortisone, levothyroxine and rhGH.

No further hypoglycemic episodes were detected during the rest of follow up. Neuro-development, and pondo-statural growth was satisfactory with catch up growth to normal height SDS and moderate bone age delay (Figure 2).

Comments.
Hypopituitarism is a chronic disease which generates considerable morbidity. It requires whole life hormone replacement therapy and specific monitoring during different life periods. ACTH-cortisol insufficiency during the first two years of life frequently results in severe hypoglycaemia during fasting which cannot be corrected without hormone replacement therapy.
On the other hand, the presence of multiple pituitary deficiencies or other signs associated to hypopituitarism such as micropenis, cryptorchidism and short stature are of help for a correct diagnosis. Clinical signs and symptoms of hypoglycaemia are secondary to CNS symptoms (paresthesia, confusion, disorientation, dizziness, incoordination, seizures, coma) and muscle disturbance symptoms (hypotonia, asthenia, tiredness), as well as symptoms associated to epinephrine secretion (sweating, pallor,
palpitations). However, in newborns and infants these signs are rather unspecific and less useful for diagnosis.

NMR imaging is very useful for diagnosis and severity of hypothalamo-pituitary abnormalities correlate with severity of hypopituitarism.

The incidence of transcription factor and signalling pathway gene mutations involved in pituitary organo-genesis identified is low, suggesting that many genes have not been identified as yet.

Figure 1

Figure 2: Clinical case 1. Graph of body length.
Patient was a term male new born who showed polycythemia and hypoglycemia during the first 24 hours of life. He was the first child of non-consanguineous parents. Placenta previa, preterm labor, and hypertension during pregnancy were reported. Mother received isoxsuprine. Delivery at 37 weeks was normal. Birth weight 2500 g (25th percentile), body length 46 cm (10th percentile), head circumference 34 cm (50th percentile), Apgar score 9-10. Family history was unremarkable.
Hypoglycemia was considered secondary to polycythemia. However, after exchange transfusion, hypoglycemia persisted, bilirubin increased to 17.4 mg/dl. Plasma electrolytes were normal. Congenital infection screening, TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes virus) and VDRL were also normal. Brain US was normal. Sepsis was diagnosed and iv antibiotics administered for 10 days. Germ cultures were negative. High requirements of glucose flux continued. Galactosemia and β-oxidation disorders were discarded.

At 15 days of age, during a new hypoglycemic episode (blood glucose 30 mg/dl) he had a serum cortisol concentration below 1 µg/dl, as well as 0.51 ng/ml serum GH, and 3.7 µUI/ml insulin. On physical examination he showed micropenis (1.5 x 0.5 cm), <1 ml scrotal testes, and anterior and posterior permeable fontanels. Secondary adrenal insufficiency was diagnosed probably due to multiple pituitary deficiencies, and he was put on Hydrocortisone treatment and frequent feeding. General condition improved.

Comments.

Persistent or recurrent hypoglycemia in stress situations, with or without seizures, is one of the more constant signs seen in infant adrenal insufficiency, as well as in GH deficiency although, less frequently [7].

Glucose requirements in the neonatal period are higher than later in life. Furthermore, hepatic glycogen reserve is scarce, being glyconeogenesis the main glucose source. This makes glyconeogenesis substrates and free fatty acids essential to maintain normal glucose levels in blood. Cortisol plays an essential role as contra-regulatory hormone in the presence of hypoglycemia. Cortisol increases glyconeogenesis and glycolisis, as well as insulin resistance. Its lipolytic and proteolytic effect contributes to generate alternative metabolic substrates.

After other causes of neonatal hypoglycaemia were discarded in this patient, secondary adrenal insufficiency was considered because of low serum cortisol and ACTH levels during hypoglycaemia and lack of hyperkalemia and hyperpigmentation characteristic of primary adrenal failure. In most instances ACTH deficiency is associated to deficiency in other pituitary hormones. In these cases, it might be the result of transcription factors mutations of one of several genes, HESX1, LHX4, LHX3, SOX3 o PROP1, active in early events of hypothalamo-pituitary organogenesis.

Less frequently, isolated ACTH deficiency might be secondary to TPIT mutations, a transcription factor member of the T-box gene family factors, required for the expression of the POMC gene and for terminal differentiation of corticotrope cells. However, in 50% of patients with isolated ACTH deficiency no mutation is found suggesting that other unknown factors are involved [8, 9].

Even though GH is important as contrarregulatory hormone, low levels of GH such, as found in this patient, during hypoglycaemia do not imply GH deficiency. It is possible that blood extraction missed a secretion pulse, or that there is a decrease in hypothalamic sensitivity to chronic hypoglycaemia [10-13].

Micropenis is a relevant clinical observation associated to GH deficiency or gonadotropin deficiency. It has been propose that GH could influence penile growth during the last trimester of gestation. Gonadotropins, particularly LH, activate interstitial Leydig cells during this period increasing testosterone secretion and stimulating penile growth.

High serum bilirubin is usual sign accompanying ACTH, GH, TSH isolated or multiple deficiencies. In the absence of treatment this could lead to cholestatic hepatitis with liver damage. Frequently this precipitates a liver biopsy. Lack of hepatic maturation in the synthesis and transport of biliary acids has been proposed as the etiopathogenesis [14]. Some causes of pituitary deficiency have been discarded in this patient, such as perinatal infections (negative TORCH) or congenital brain tumor (normal brain US).
Further studies of pituitary function showed: TSH 10.2 µIU/ml, T4 2.33 µg/dl and T3 0.97 ng/ml, indicating central hypothyroidism. He was put on 50 µg/day levothyroxine and he further improved his general condition and the skin abnormalities, as well as temperature regulation. Serum prolactin: <1 ng/ml (Normal 15-30), IGF1: 18.5 ng/ml (Normal 40-150) and IGFBP3: 0.75 µg/l (Normal 1.3-4). were all low.

Comments.

Signs and symptoms of central hypothyroidism associated with hypothalamo-pituitary insufficiency are the same as in primary hypothyroidism, even though less severe because of residual TSH secretion, with the exception of TSH receptor or β-TSH subunit mutations. In this patient, jaundice, permeable posterior fontanelle and thermal instability suggested hypothyroidism. Finally serum TSH, even though slightly increased was inappropriate for the low levels of serum T4, confirming the diagnosis of central hypothyroidism. Pediatricians should be alert to diagnose central hypothyroidism since these patients are not detected by TSH-based screening.

Very low serum prolactin levels suggest lactotrophic insufficiency. Association of TSH, GH and prolactin deficiency has been described in POU1F1 (PIT1) mutations. This factor is expressed late in pituitary development and it is necessary for somatotrophic, lactotrophic and thyrotrophic development. So far, our patient has shown deficiencies in at least 3 pituitary functions: ACTH, TSH, Prolactin. On this basis gene candidates for mutations would be HESX1, LHX4, LHX3, SOX3 or PROP1.

Patient was discharged at 30 days of age. He had good tolerance to fasting. Weight 2600 g (SDS -2.53), body length 47 cm (SDS -3.76) (Figure 3), head circumference 34 cm (3rd percentile). A wide anterior fontanel was observed. At 3 months of age, he was in good conditions, Neurologic maturation was normal for age. Weight 4400 g (he was improving at 29 g/day), body length 53.2 (SDS -3.47), growth velocity 28.8 cm/year, head circumference 38 cm (3rd percentile). Somatotrophic function was tested with arginine stimulation, and showed low GH values in all samples. Thyroid hormones were TSH <0.05 mUI/ml, T4 18.6, T3 1.56 ng/ml, requiring dose adjusting. Serum FSH was <0.10mIU/ml, serum LH<0.10 mIU/ml, and serum Testosterone < 0.1 ng/ml. These studies confirmed the diagnosis of GH deficiency and lack of minipuberty. Brian NMR showed pituitary hypoplasia and ectopic neurohypophysis.

Comments.

As previously discussed, GH concentration during spontaneous hypoglycemia is not a very specific sign for diagnosis of GH deficiency. On the other hand, rhGH administration was necessary, along with glucocorticoids, to revert hypoglycemia. Moreover, during the first 6 months of life body growth is scarcely dependant of GH, making GH deficiency difficult to confirm. In this patient, the arginine stimulation test supported GH deficiency diagnosis, since serum GH was low at all times tested.

In normal boys, there is a postnatal activation of the gonadotrophic-gonadal axis (minipuberty). There is a transitory elevation of serum gonadotropins and of testicular testosterone. The physiologic role of this early activation of the hypothalamo-pituitary-gonadal axis is not clear but it could prepare the testis for future function (fertility). This early stimulation phase is convenient for the diagnosis of potential hypogonadotropic hypogonadism. In our patient, the clinical evidence (micropenis)gonadotrophic insufficiency was supported by the undetectable levels of serum gonadotrophins and testosterone.
Hypothamic: pituitary NMR imaging is an useful tool for diagnosis. Many alterations have been described: pituitary hypo or hyperplasia, pituitary stalk agenesis, absent or ectopic neuro-pituitary, anomalies of the infundibulum. Other associated anomalies are: hypoplasia or agenesia of the corpus callosum, septum pellucidum or optic nerve or chiasm. Other: holoprocencephalia, equizencephalia, cerebellar hypoplasia, fornix aplasia, Chiari malformation. A high correlation between neuro imaging anomalies and severity of pituitary deficiency has been reported. According to a recent report [15] the risk of hypopituitarism is 27.2 times greater in patients with ectopic neurohypophysis. Anterior pituitary hypoplasia and absence of corpus callosum are also associated with functional hypopituitarism.

Treatment with 0.5 UI/Kg.day rhGH was initiated at 8 months of age, when body length was 60.5 cm (SDS -4.2) and weight was 6820 g (SDS -1.86). IM testosterone (2 mg/Kg, every 30 days for 3 months) was also indicated to stimulate penile size; a good response was observed. At 10 months of age, acquired bilateral cryptorchidism was found. He received hCG treatment in three occasions, but only the left testis descended to the scrotum; therefore, a right orchidopexy was carried out.

Comments.
Testicular descent in humans is normally completed before birth. Two phases have been described: 1) transabdominal and 2) inguinal. In the transabdominal phase the testis remains attached to the internal inguinal orifice by the gubernaculums. At this stage, a peptide hormone, INSL3, a hormone secreted by testicular Leydig cells, plays a central role. During the second phase, the testis is guided to the scrotum by the gubernaculum. This phase is androgen dependent.
Undescended testis and micropenis are frequent findings in hypogonadotrophic hypogonadism. Curiously, our patient had a normal testicular descent, but surprisingly a post natal bilateral ascent took place at 10 months of a, 2 months after the onset of rhGH treatment, notwithstanding his hypogonadotropic hypogonadism. Acquired cryptorchidism has been described in school age boys, probably because of lack of adequate sperm cord elongation during growth [16]. We might propose the hypothesis that rhGH-induced somatic growth was not associate with a parallel growth of the spermatic cord.
Cryptorchidism is treated by either surgery or hormonal stimulation, the latter base on the hypothesis of a disorder of the hypothalamo:pituitary:gonadal axis. Most recent reports recommend surgical treatment early in life. In our patient hormonal treatment was not successful and orchidopexy was indicated.

During follow up there was a good growth response to rhGH therapy with a catch up of height SDS. At 12 years, 10 months of age, bone age was 9 years and volume of the two scrotal testes was 1 ml. Growth velocity though was below the 3rd percentile. Laboratory studies revealed LH 0.15 mIU/mL, FSH <0.10 mIU/mL and testosterone <0.05 ng/mL. Presumptive diagnosis of hypogonadotrophic hypogonadism was made. For this reason and because growth velocity had decreased under rhGH therapy, monthly 25 mg IM testosterone was started. Improvement in growth velocity occurred.

Comments.
The diagnosis of hypogonadotrophic hypogonadism was strongly suspected by the micropenis and the absence of minipuberty. Recently, the detection of low FSH levels has been proposed as a good test for the diagnosis of hypogonadotropic hypogonadism [17]. In boys (similar to girls) estrogens secreted by the gonad (testis, 20%) or synthesized in peripheral tissues (80%) is critical for skeletal maturation and the
pubertal growth spurt. Estrogens stimulate chondrogenesis in the growth plate, and contribute to its final closure [18]. For this reason, it has been speculated that in isolated GH deficiency with spontaneous puberty final height is greater than in patients with associated hypogonadotropic hypogonadism. However, many studies have shown that final height is directly related to height at onset of puberty and not to age at onset of puberty; therefore it is very important to optimized prepubertal growth. On the other hand, induction of puberty at a physiologically adequate age does not alter final height in patients with multiple pituitary deficiencies [19, 20].

Last control, at 14 years old, showed a 11years, 3months bone age, 59.3 Kg weight (SDS 0.60), 157.9 cm height (SDS -0.2), 6.9 cm/year growth velocity, and sexual development Tanner’s stage II with 1 ml scrotal testes. Present treatment: rhGH, levothyroxine, oral hydrocortisone and IM testosterone.

Comments. The irreversible nature of these congenital deficiencies requires different replacement therapies at different life stages. Replacement therapy with thyroid hormone and glucocorticoids are necessary for the whole life, and it is necessary to increase corticoid dose during stress situations. Replacement therapy for GH deficiency is required during somatic growth, but it is controversial whether rhGH treatment is required to improve metabolic homeostasis (at lower doses) later in life. In the case of gonadotropic insufficiency it is necessary to induce sexual development at puberty with testosterone at increasing doses. This treatment should be maintained during the whole sexual life. This treatment, however does not stimulate spermatogenesis, which need to be induced with LH/FSH. Treatment of infertility is complex and it is outside the scope oh this review.
GENERAL DISCUSSION.
Signs and symptoms of hypothalamo-pituitary deficiency are secondary to different hormonal deficiencies and, in general, are unspecific during the neonatal period. Neonatal hypoglycemia associated to prolonged jaundice, midline alterations, nistagmus, micropenis or cryptorchidism should prompt to study pituitary function thoroughly in order to confirm or not the diagnosis of hypothalamo-pituitary deficiency. An early treatment might prevent death or severe brain damage.

An original recent publication provides reference values and a diagnostic cutoff for the GH levels in newborns at the age between day 3 and 5 [21]. GH was measured in the eluate from filter papers of the newborn screening test. They provide data supporting the possibility that in the presence of clinical evidence, the diagnosis of neonatal GH deficiency can be confirmed during the first week of life by a single randomly taken GH level less than 7 µg/liter, with 100% sensitivity and 98% specificity. Moreover, the diagnostic approach can use stored screening cards, a very practical and convenient possibility.

In the last decade, important advances have been made in the knowledge of genes involved in pituitary organogenesis. These advances will hopefully allow to understand phenotypic differences, and to improve morbid-mortality and therapeutic decisions.

Pituitary organogenesis is a complex process starting in the human between the 5th and 6th week of gestation. The anterior pituitary originates from an invagination of the primitive oral ectoderm (Rathke’s pouch) and makes contact with part of the primitive diencephalon (neural ectoderm). Signal molecule cascades and several transcription factors will stimulate or repress multiple genes to differentiate organs in a coordinate way. The final pituitary product will be the differentiation and proliferation of five specialized cell types of the anterior pituitary [22].

Studies in animal models, and gene mutations described in humans of a complex genetic cascade of transcription factors and signaling molecules, have clarified many of the interruptions of the process of hypothalamo-pituitary organogenesis resulting in variable phenotypes from isolated or multiple pituitary insufficiency to more complex disorders such as septo-optic dysplasia or holoprosencephaly.

Even though mutations in several genes have been described, in most instances the etiology of hypothalamo-pituitary deficiencies remains unknown. In the case of these patients candidate genes are the listed as follows:

**PROPI.** It is a transcription factor which represses HESXI and activates POU1f1. The gene is located in chromosome 5q35 and it has an autosomic recessive mode of transmission. It is the most frequent mutation found in multiple pituitary deficiency. Deficiencies are expressed early (GH, TSH, Gonadotropins) or late (ACTH). NMR imaging might show a normal, hypoplastic or hyperplastic pituitary, but not ectopic neurohypophysis.

**HESXI.** It is a repressor transcription factor localized in chromosome 3p14.3. It has an autosomal dominant or a recessive mode of transmission. It is expressed early in pituitary embryogenesis, it has a fundamental role in pituitary gland and forebrain determination and differentiation. Dattani et al. [24] described a homozygotic HESXI mutation in two siblings with severe septo-optic dysplasia and hypopituitarism. NMR imaging showed hypoplasia of the antero-hypophysis, ectopic neuro-hypophysis, corpus callosum and septum pellucidum agenesia. Similar to the mouse experimental model there is no clear genotype-phenotype correlation in humans. HESXI mutations produce variable pituitary deficiencies, from isolated GH deficiency to multiple deficiency and septo-optic dysplasia [25, 26].

**LHX3.** It is a transcription factor expressed early in development localized in chromosome 9q34.3. It has an autosomal recessive mode of transmission. Most patients had multiple pituitary deficiency, but milder forms have also been described. Many patients have a limitation in neck rotation and variable degrees of neuro-sensorial
deafness. Hypopituitarism without neck abnormalities have been described [27]. NMR imaging shows pituitary hypoplasia or adenoma-like enlargement. The neurohypophysis is normal.

**LHX4.** In close relationship with LHX3, it is expressed in brain and neural cord. The gene is localizize to chromosome 1q25.2. It has an autosomal dominant mode of transmission. GH, TSH, gonadotropin and ACTH deficiencies have been described. NMR imaging: pituitary hypoplasia with or without ectopic neuro-hypophysis, cerebellar abnormalities, Chiari malformation [28].

**SOX3.** Early marker of progenitor stem cells, its expression decreases when cell differentiation progresses. The gene is localized in chromosome Xq27.1, X-linked mode of transmission. Both sub and overexpression determine multiple hypopituitarism or isolated GH deficiency, with or without mental retardation. NMR imaging: ectopic neurohypophysis, infundibular hypoplasia, corpus callosum abnormalities [28].

**OTX2.** The gene is localized in chromosome 14p22. It is required for anterior brain and eye development. Microdeletions are associated to hypopituitarism and ophthalmic abnormalities. A recent paper has described two patients with multiple pituitary deficiency, pituitary hypoplasia, ectopic neurohypophysis without eye alterations. A dominant negative effect on HESX1 has been proposed [29].

**TABLE 1.**

<table>
<thead>
<tr>
<th>gene</th>
<th>Localization</th>
<th>Hormona Deficits</th>
<th>NMR imaging</th>
<th>Other characteristics</th>
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<td>PROP1</td>
<td>5q35</td>
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<td>AH:p PH:ec</td>
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**REFERENCES.**

See Spanish version