CLINICAL CASE PRESENTATIONS OF THE ENDOCRINOLOGY
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DISORDERS OF PUBERTY AS INITIAL SIMPTOM OF CENTRAL
NERVOUS SYSTEM PATHOLOGY

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CLINICAL CASE 1

A 5.5-year-old boy was admitted to the Hospital because of penile growth, pubic
hair, and deep voice during the last 6 months. The patient was born after a full-term
gestation, without complications.

On examination, the patient appeared well. The height was 112.4 cm (SDS +2.34),
the weight 20 kg (SDS +0.07), deep voice, Tanner’s stage 3 pubic hair, stage 4 genitalia, 3
ml/3 ml testicular volume, located in the scrotum. Bone age was 5.8 years (not advanced).
Therefore, development of external genitalia in the presence of lack of testicular growth
suggests Pseudo-precocous Puberty, secondary to the following potential diagnoses:

1. Congenital adrenal hyperplasia (CAH)
2. Testicular or adrenal virilizing tumor
3. hCG producing tumor
4. Testotoxicosis.

Additional studies were as follows: serum LH 0.10 U/L, FSH 0.16 U/L, and testosterone
(T) 2.39 ng/ml. These data confirm a diagnosis of gonadotropin-independent precocious
puberty: (normal values (NV) for LH: 0.78 ± 0.99 UL/ml, FSH: 2.26 ± 0.96 U/L, T: < 0,25
ng/ml); serum 17OHP4 level was 1.37 ng/ml (NV: 0.20 ± 0,80 ng/ml), rejecting CAH as a
diagnosis. Normal levels of DHEAS (180 ng/ml) suggested that probably no adrenal tumor
was present. Testis and adrenal ultrasound were normal.

Other symptoms were enuresis, polyuria and polydipsia. Rate of Diuresis (4.9
ml/Kg/hour), hypostenuria (urine density: 1005), and hypernatremia (Na: 148 mEq/L) were
consistent with the diagnosis of diabetes (DBT) insipidus. Patient was put on 0.1 mg/day
desmopressin, with good response.

In this patient the association of pseudo-precocious puberty and DBT insipidus
suggests hypothalamic hCG producing tumor.

Serum hCG was 18.8 U/L (NV 5 U/L), cerebrospinal fluid hCG was 35.5 U/L
Brain MRI showed pituitary stalk enlargement, absence of neurohypophysis and moderate adeno-hypophysis enlargement. With the clinical diagnosis of suprasellar germ cell tumor, chemo- and radiotherapy was implemented, with excellent response.

CLINICAL CASE 2

A 10.7-year-old boy with complete pubertal development was admitted to the Hospital because of headaches and decreased right visual acuity of approximately 3 year duration.

On examination, the weight was 48 Kg (SDS +1.44) and the height was 150 cm (SDS +1.67). He had Tanner's stage 4 pubic hair, an adult penis, 25/20 ml testicular volume, ++++ axillary hair, and deep voice.

Presumptive diagnosis was Central Precocious Puberty secondary to a CNS tumor. An ophthalmologic evaluation revealed right eye (RE) atrophic papilla, left eye (LE) optic disk pallor and decreased visual acuity. A MRI study showed a sellar and suprasellar mass extending to medium and anterior fossa and to the hypothalamic region.

Pre-surgery laboratory studies showed a pubertal gonadotropin response to LH-RH (Maximum peak LH 17 U/L, NV for a pubertal response LH > 9.6 U/L) and a serum T level of 3.4 ng/ml (pre-pubertal T NV 0.05-03 ng/ml), confirming, thus, the diagnosis of gonadotropin-dependent Central Precocious Puberty. Serum tumor markers -Fetoprotein and hCG were negative (NV < 3 ng/ml and < 5 U/L, respectively), and the rest of pituitary function was normal, TSH 4.12 U/L, T4 8.6 µg/dl, T3 1.73 ng/ml (NV TSH: 0.40-5.8 U/L, T4: 5.5-13.1 µg/dl), Prolactin (PRL) 14.7 ng/ml (NN 5-25 ng/ml), maximum serum GH after Arginine stimulation 12.9 ng/ml, (NV maximum serum GH in stimulation tests > 6.4 ng/ml). Serum cortisol was 5.1µg/dl. Since it was not possible to evaluate adrenal function before surgery, hydrocortisone treatment was started receiving 60 mg/m²/day for surgery.

At surgery, only partial tumor removal (50%) was achieved to avoid further damage to the left optic nerve and chiasm. Pathological diagnosis: low grade Pilocytic astrocytoma. A post-surgical report informed presence of ocular movements and photomotor reflex. Visual acuity: RE 20/20 at 20 cm with papillary atrophy, RE 20/20 at 3 meters. One month after surgery pituitary function was normal. Serum T remained elevated (2.03 ng/ml), bone age was 14 years (chronological age 11.3 years) and height 153.1 cm (SDS +1.59). Therefore, LHRH analog was indicated in an attempt to improve final height.
CLINICAL CASE 3

A 2.56-year-old boy was admitted to the Hospital because of a 1 year increase in penile size and growth velocity. The patient was born after a full-term gestation and received 4-day phototherapy because of jaundice. He had 5 febrile episodes of seizures during his first year of life. He presented pneumonia at 2 months of age, as well as 6 acute bronchospasm episodes during his first year of life.

On examination the weight was 22.6 Kg (SDS +4.76), the height 108.4 cm (SDS +4.42), and 120% relative weight. He presented pubic lanugo, Tanner’s stage 3-4 genitalia, and $8/8$ ml testes in the scrotum. Bone age was 5 years. Gonadotropin-dependent Central Precocious Puberty was suspected because of sexual development in the presence of testicular enlargement. Laboratory tests showed a pubertal response to LH-RH test: maximum LH 28.6 U/L, maximum FSH 6.84 U/L (NV LH > 9.6 U/L) and a high serum T level, 1.78 ng/ml (NV < 0.25 ng/m, for prepubertal age), confirming the diagnosis of Central Precocious Puberty. The rest of pituitary function was normal. Patient’s age and the short evolution of puberty made central puberty secondary to previous peripheral puberty unlikely. Clinical history of early seizures of dubious etiology suggests a congenital organic CNS lesion.

The MRI study revealed a 1.2 x 1.3 mass close to the pituitary and optic chiasm, showing low intensity in T1 and high intensity in T2, reinforced by the paramagnetic contrast. There was an apparent displacement of the pituitary stalk. A presumptive diagnosis of Hypothalamic Hamartoma was made. Ophthalmologic evaluation was normal.

In order to inhibit pubertal progression, and to improve final height and psychological adaptation in this young boy, LH-RH analog therapy was initiated with good clinical response.

CLINICAL CASE 4

A 14.4-year-old boy was admitted to the Hospital because of pubertal delay. The height was 155.4 cm (SDS -0.68), weight 46.5 kg (SDS -0.7), growth velocity 2.8 cm/year. Body mass index was 20.39 (SDS +07), testis volume 2/2 ml, genitalia and pubic hair Tanner’s stage 1 of sexual development. His clinical condition had deteriorated during the previous 3 years, presenting weakness, anorexia and weight loss (25-30 Kg). Clinical studies failed to reach a diagnosis. Bone age was 13 years and a X-ray film showed an enlarged sella without calcifications.

Laboratory studies showed low gonadotropin and testosterone serum levels for sex and age, LH: 0.29 U/L; FSH: 0.31 U/L; testosterone [T]: < 0.10 ng/ml (T pubertal: 2.2-8
ng/ml), and prepubertal response to LH-RH, maximum LH 1.58 U/L, maximum FSH 1.04 U/L (normal LH response > 9.6 U/L); serum TSH 2.13 U/L, T4 4.86 µg/dl, T3 0.92 ng/ml (NV, TSH: 0.40-5.8 U/L, T4: 5.5-13.1 µg/dl) consistent with central hypothyroidism, high serum prolactin 63 ng/ml (NV: 5-25 ng/ml), hypocortisolism, 8-hour cortisol 1.9 µg/dl (NV 5-25 µg/dl). Pharmacological tests of GH secretion showed deficient responses: maximum level after arginine was 1.49 ng/ml and after clonidine 1.36 ng/ml (NV > 6.4 ng/ml). These studies indicate multiple pituitary hormone deficiency. High Prolactin levels suggest presence of a sellar or supra-sellar organic lesion affecting pituitary stalk, and depriving prolactin-secreting cells of dopamine inhibition. In these cases, prolactin levels usually do not exceed 150 ng/ml. Higher levels suggest a macro-prolactinoma.

MRI showed an intrasellar and suprasellar mass compressing the optic chiasm. The mass included a T1 hyper-intense lesion compatible with hemorrhage suggesting a hemorrhagic macroadenoma. However, since prolactin levels were not high enough the lesion could correspond to a non-functioning adenoma. Ophthalmologic examination revealed bitemporal hemi-anopsia. Patient was put on hydrocortisone and levothyroxine. Surgical removal of the tumor was carried out. Pathological diagnosis was craniopharyngioma. After surgery, multiple pituitary deficiency persisted and central diabetes insipidus was added.

**DISCUSSION**

Usually, an increase in testicular volume (> 3 ml) is the first measurable clinical sign of puberty in boys. This takes place between 9 and 14 years of age, mean 11.5 years. On the other hand, a mammary budding is the first clinical sign in girls (Tanner’s stage II), taking place between 8 and 13 years of age, mean 10.8 years. Therefore, when puberty starts after 9 years in boys and after 8 years in girls a diagnosis of **precocious puberty** is made, and when it has not started at 14 years of age in boys and at 13 years of age in girls a **pubertal delay** is diagnosed.

Hypothalamic GnRH pulse generator is a central element in the neuro-endocrine integration of pituitary gonadotropin (LH and FSH) secretion. Initiation of puberty results from multiple maturation changes in the central nervous system which follow a precise progressive order, involving neuronal and glial circuits bound to the GnRH neuron.

Many pathological processes of the central nervous system (CNS), particularly in the hypothalamic region, can manifest themselves as disorders of puberty. CNS tumors are the second most frequent oncolologic disease in childhood, and sellar and supra-sellar tumors account
for 10-15% of them (1-3). The four cases discussed in this report illustrate different clinical presentations of pubertal disorders secondary to CNS tumors. The different mechanisms of these lesions will be discussed.

**Central Precocious Puberty (GnRH-dependent)** implies the premature activation of GnRH-producing hypothalamic neurons, and it may be associated to glial tumors or hypothalamic hamartomas. Presumably astro-glial growth factors are involved in the facilitation of the activation of GnRH neuronal system (4).

**Pseudo-precocious puberty (GnRH-independent)** is the early production of sex hormones without activation of the hypothalamic-pituitary-gonadal axis. It can be central (hCG tumors) or peripheral (adrenal, gonads, etc).

**Pubertal delay** associated with CNS lesions is mainly secondary to hypothalamo-pituitary compression, infiltration or destruction in this region depending on the primary lesion. Neurologic or ophthalmologic disorders can be associated, as it is seen in cranipharyngiomas and other sellar or supra-sellar lesions. Prolactinomas can also induce Pubertal Delay by compression/destruction (macroprolactinomas) or by hypothalamic deregulation secondary to high prolactin levels. It is also important that pubertal disorders secondary to organic lesions can manifest as lack of progress or regression of puberty.

We will briefly discuss the clinical cases presented and disorders of puberty.

**Hypothalamic Hamartoma (HH):** HH are congenital non-neoplastic lesions of heterotopic nervous tissue similar to hypothalamic gray matter. They are formed by neurons, glial cells and neural fibers, localized to the third ventricle close to the tubercinerium and mammillary bodies (5).

Clinically they show central precocious puberty and seizures (gelastic crisis, atypical absence). These seizure episodes are observed at 2-3 years of age, and they can be associated to cognitive or behavioral disorders. Hypothalamic hamartomas are the most frequent etiology of organic central precocious puberty, and they are usually seen at earlier ages than idiopathic precocious puberty (5). Onset of puberty is usually observed before 4 years of age and other hypothalamo-pituitary functions are preserved. The detection of a sessile or peduncle isodense gray substance, at a brain MRI is diagnostic of hypothalamic hamartoma.

Two hypotheses have been proposed to explain HH associated central precocious puberty. The first proposes the presence of GnRH neurons in the mass functioning as heterotopic GnRH pulse generators. The second involves presence of TGF-β and erbB-1 receptor in astroglial cells which positively affect the GnRH neuronal system. TGF-β would act through neural fibers to initiate puberty when it is secreted in close proximity to the
GnRH pulse generator (Figure 1). (5)

Therefore, in HH symptoms will depend not only of cell composition but also of morphology and position relative to other hypothalamic structures. Intra-hypothalamic location, third ventricle dystorsion and male sex are strongly associated to seizure episodes, while para-hypothalamic location is associated with central precocious puberty affecting ventral hypothalamus, associated to the GnRH area. (4)

GnRHa therapy is used for precocious puberty, and anti-epileptic medications for seizures. Eventually resistant seizures will require radiosurgery (5).

**Glioma/Astrocytoma:** Glioma is a subtype of neuroepithelial tumor derived from glia cells. They can be found in brain hemispheres, cerebellum, hypothalamus, optic chiasm and optic nerves. Pilocytic astrocytoma is the main histological sub-type among hypothalamo-chiasm tumors. It is a usually benign with good long-term prognosis (6-9).

Polimixoid astrocytoma is more aggressive variant of pilocytic astrocytoma observed in younger patients (mean age 18 months) (10). It is preferentially located in the hypothalamus (11).

Optic tract gliomas represent 5% of CNS tumors in pediatrics. They are most commonly observed during the first decade of life. They are observed in 10-30% of patients with type 1 neurofibromatosis, usually located in optic nerves. They are benign, multifocal and bilateral (6-8). Ophtalmologic compromise is the most frequent clinical presentation in patients with hypothalamic-chiasmatic tumors (7). Central precocious puberty is seen in 18% of suprasellar glial tumors (12). It is usually a rapidly progressive puberty, but it is only seen when it is located close to the hypothalamus or to the GnRH neuronal red. It has been suggested that this process pubertal tempo advancement would involve TGF- and prostaglandin E2 (Figure 2).

The characteristic MRI is an iso- or hypointense image in T1 and hypertense one in T2, reinforced with gadolinium.

At present, a conservative approach is recommended for treatment of these tumors, avoiding radiotherapy because of the known adverse effects in small children, using chemotherapy in patients with progressive diseases, and surgery when absolutely indispensable.

**Germ cell tumors (GCT):** Germ cell tumors are classified in Germinomas and nongerminomatous (NGGCT) tumors on the basis of histology and degree of differentiation. Germinomas are the most frequent group (50-70%), and they are non-differentiated uni-potential cells similar to primordial germ elements. NGGCT include choriocarcinomas, endodermal sinus tumors (yolk-sac tumors), embryonary carcinomas,
and mixed tumors. Some of these tumors secrete specific markers, such as \( \text{AFP} \) and \( \text{hCG} \), which might be detected in blood or CSF and are useful diagnostic and follow-up tools (13). Intra-cranial GCT are frequently localized in the pineal or suprasellar regions, and they are responsible for 0.4 to 3.4% of CNS tumors in pediatrics (6,13). An exclusive pituitary stalk localization has been reported, manifested by a widening of the stalk occasionally associated with diabetes insipidus. This association has to be differentiated from Langerhans histiocytosis or hypophysitis (13).

Initial symptoms depend on tumor localization and size. Patients with suprasellar GCT frequently show signs of hypotalamo-pituitary dysfunction such as diabetes insipidus (49-90%), pubertal delay or central precocious puberty, and hypopituitarism, along with ophthalmological disorders, such as bi-temporal hemianopsia (14-15). In pediatrics, GCT tumors are frequently associated with diabetes insipidus, which might precede several years the detection of an abnormal intracranial MRI. Therefore, an annual MRI checkup is recommended in idiopathic diabetes insipidus children (13).

\( \text{hCG} \) secreting GCT can produce male central precocious puberty. \( \text{hCG} \) stimulates steroidogenesis after binding to the LH receptor in Leydig cells, generating precocious puberty with dissociation between body virilization and testis volume (Figure 3) (14-15).

Treatment of GCT depends on the histological nature of the tumor but in general is a combination of radiotherapy and chemotherapy. Pure germinomas are very radiosensitive. The addition of chemotherapy to radiotherapy has allowed for a lower radiation dose which decreases morbidity. NGGCT are less sensitive to radiotherapy (6,14,16).

**Craniopharyngioma:** These tumors constitute a rare sella area malformation with low malignancy characteristics originated in cranio-pharyngeal duct. They account for 1.2-4% of all intracranial tumors in childhood (17-20).

Usually initial symptoms are related to increased intracranial pressure: headaches, nausea and vomits. Ophthalmological lesions are frequent (62-84% at onset of clinical symptoms) (17-19,21). Symptoms related to endocrine dysfunction are also frequent secondary to compression, infiltration or destruction of the hypothalamo-pituitary area (Figure 4): short stature, hypothyroidism or lack of pubertal development (6-10). GH secretion is most frequently affected (75-90%) Deficiencies in other functions have been estimated as follows: \( \text{LH-FSH} 40-60\% \), \( \text{ACTH} 25\% \), \( \text{TSH} 25-65\% \) and \( \text{ADH} 17-18\% \) (18-21).

The most frequent alteration in cranial x-ray films is the calcification of the sellar
floor. For this reason, a cranial x-ray is recommended in all children with growth retardation since this clinical sign might become evident long before neurological or ophthalmological signs, making then possible a much earlier diagnosis. This is of great pediatric clinical relevance since it will result in an earlier diagnosis, simpler treatment and lower morbidity. MRI is very important for diagnosis, topographic localization and estimation of hypothalamic involvement (17, 20).

Treatment is surgical removal of the tumor with or without radiotherapy.

**Prolactinoma:** Prolactinomas are pituitary adenomas derived from lactotropic cells, characterized by the hypersecretion of prolactin. Even though pituitary adenomas are the most frequent pituitary lesion in adults, they are not frequent in childhood. There is however an increase in adolescence, representing around 2% of intracranial tumors (22).

Similar to adults, prolactinomas are generally benign and more frequent in girls. They are classified in microprolactinomas (diameter 10 mm), macroprolactinomas (diameter 10 mm), and giant macroprolactinomas (diameter 40 mm). Microprolactinomas are more frequent in girls while macroprolactinomas are more frequent in boys (23). Clinical manifestations of prolactinomas result from hyperprolactinemia, by alteration of GnRH pulsatility, LH and FSH inhibition and directly gonadal steroidogenesis (23). In adult women, microadenomas mainly induce primary or secondary amenorrhea and galactorrhea, and less frequently by tumor compression by a large tumor (24). Decreased bone mineral density is observed secondary to hypogonadism-induced hyperprolactinemia (23, 26).

In prolactinomas, serum prolactin usually exceeds 200 ng/ml, and other clinical signs are mostly related to tumor growth, such as headaches, and alterations in visual acuity or visual fields. In children, macroprolactinomas are present in a higher proportion than in adults; symptoms include pubertal delay in the two sexes, and primary amenorrhea and galactorrhea in girls. Due to the high frequency of macroprolactinomas, ophthalmologic disturbances (decreased visual acuity, bitemporal hemianopsia) are secondary to suprasellar growth and tumor damage to the optic chiasm (23-27). Clinical manifestations in boys include pubertal delay, ginecomastia, galactorrhea, and more frequently than in adults, neuro-ophthalmological signs.

Diagnosis of prolactinoma, not only requires radiological evidence of a pituitary tumor, but also measurement of sustained serum hyperprolactinemia, provided other causes of prolactinemia have been excluded (27). It must be mentioned that hyperprolactinemia and pituitary tumor are not enough for the diagnosis of prolactinoma, since other pituitary masses can induce hyperprolactinemia by interrupting the permanent
negative dopamine tone reaching the pituitary from the hypothalamus (23, 24, 27).

The main aim in the treatment of micro-prolactinomas is to normalize serum levels of prolactin in order to restore gonadal function, and secondarily reduce tumor size (23). In the absence of signs requiring an immediate surgical intervention, such as gradual vision loss, hydrocephaly, etc., treatment with dopamine agonists (cabergoline, bromocriptine, etc.) is the first line of treatment (26, 27). Surgical treatment is indicated in cases of dopamine agonist resistance or severe neurologic symptoms at diagnosis. Radiotherapy could be indicated in aggressive tumors with high risk of neurological damage or panhypopituitarism.

In our experience at Garrahan Pediatric Hospital, we have studied neuro-ophthalmological alterations and endocrine function in 309 patients with CNS lesions of the sellar and suprasellar regions. Most lesions were diagnosed during pre-puberty (PP) (73.4%), while 26.6% were diagnosed during puberty (P). In PP, tumor type frequency was: Glial cell tumors 34.3%, craniopharyngioma 30.8%, germ cell tumors 11.4% and hypothalamic hamartomas 7.9%. Hamartomas and glial cell tumors were seen in younger children. In P, craniopharyngiomas (29.9%) and prolactinomas (34.14%), were the most frequent etiologies, the latter most frequently seen in adolescent girls. In relation with pubertal tempo, 89% of hamartomas and 10.3% of hypothalamic glial tumors showed central precocious puberty. Morerover, 80% of patients with germ cells tumors showed pseudo precocious puberty. On the other hand craniopharyngiomas mainly showed signs secondary to compression or destruction of neighboring cerebral structures: hypogonadism, visual alterations and signs of intracranial hypertension.

CONCLUSION: Multiple pathological processes acting through different mechanisms which affect the CNS, particularly in the hypothalamic region, can manifest diverse pubertal disorders. Therefore, careful examination of pubertal signs is a valuable tool for diagnostic orientation in these different pathologies.

FOR FIGURES SEE SPANISH VERSION

REFERENCES:


