Ussefulnes of imaging techniques in the diagnostics of precocious puberty in boys

Anna Jakubowska¹, Magdalena Grajewska-Ferens², Michał Brzewski¹, Barbara Sopyło³

¹ Department of Pediatric Radiology, Medical University of Warsaw, Warsaw, Poland
² Department of Pediatric Endocrinology, Medical University of Warsaw, Warsaw, Poland
³ Department and Clinic of Pediatric Hematology and Oncology, Medical University of Warsaw, Warsaw, Poland

Author’s address: Anna Jakubowska, Department of Pediatric Radiology, Medical University of Warsaw, Marszałkowska 24 St., 00-568 Warsaw, Poland, e-mail: a.jakubowska@evbox.pl

Summary

Background: Precocious puberty (PP) is defined as the appearance of symptoms of puberty in girls before 8 years of age and in boys under 9. Statistically, it occurs much more frequently in girls, while it is a rare pathology in boys.

Material/Methods: Over the period of 10 years, between 1999 and 2009, 39 girls and 17 boys aged 18 months – 9 years were diagnosed with precocious puberty, and treated at the Endocrinology Clinic.

The following tests were performed in all children: physical and anthropometric examinations, abdominal ultrasound scan (US) with evaluation of adrenal glands, examination of testes in boys or breasts and pelvic organs in girls, evaluation of skeletal age and, in selected cases, CT scans of the abdomen, MRI of the CNS, and hormonal laboratory tests.

Results:

In the group of 17 boys the findings included: gonadotropin –dependent central puberty in 6 boys: idiopathic in 5 cases, and 1 case of a brain tumor – astrocytoma.

Gonadotropin-independent precocious pseudopuberty was diagnosed in 11 boys: congenital adrenal hyperplasia in 5; in 1 case – hyperandrogenism caused by overactivity of 5-α reductase; in 2 subjects – adrenal adenoma; in 2 boys adrenocortical carcinoma was diagnosed and Leydig cell tumor of testis in 1.

Conclusions:

1. Precocious puberty occurs less often in boys, but in our population it was found in 17 boys of 56 treated children, which constituted as much as 30%. 2. Precocious pseudopuberty was found in 64% of the boys with PP. 3. Adrenal and testicular tumors were the causes of precocious puberty in the youngest group of boys aged 18 months – 6 years.

Key words: precocious puberty • boys • diagnosis

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Background

Puberty is characterized by growth acceleration and development of secondary and tertiary sexual characteristics. Physiological puberty is a consequence of maturation of the hypothalamic-pituitary-gonadal axis. The first sign of sexual maturation in girls is enlargement of mammary glands while in boys – testicular enlargement. It is considered precocious if symptoms of puberty appear before the age of 8 in girls and 9 in boys. Signs of precocious puberty (PP) may be caused by severe disorders, hormonal imbalance, or often, neoplastic diseases. They raise reasonable concern and always require quick and thorough diagnosis and treatment.

Material and Methods

Material

Over a period of 10 years, from 1999 until 2009, 56 children including 39 girls aged 3–8 years and 17 boys aged 18
months – 9 years were diagnosed and treated due to preco-
cocious puberty at the Endocrinology Clinic (Table 1).

Methods

All children underwent physical and anthropometric exam-
inations with growth assessment, abdominal ultrasound
scan with examination of adrenal glands, testes in boys,
mammary glands and organs of the lower pelvis in girls, as
well as x-ray assessment of skeletal age. In selected cases,
magnetic resonance imaging of the central nervous sys-
tem, abdominal CT and hormonal laboratory studies were
performed.

Results

Precocious puberty was diagnosed in 39 girls. In this
group there were 36 girls with central idiopathic GnRH-
dependent PP, 3 with peripheral GnRH-independent preco-
cocious pseudopuberty, 1 case of an estrogen-releasing adre-
nal adenoma and 2 cases of ovarian cysts.

In the group of 17 boys, central gonadotropin-dependent
PP was diagnosed in 6, idiopathic GnRH-dependent PP
in 5, and CNS tumor (astrocytoma with history of von
Recklinghausen disease) in 1.

Peripheral, GnRH-independent precocious pseudopuberty
was diagnosed in 11 boys: congenital adrenal hyperplasia
in 5 cases, elevated androgen levels due to the overactivity
of 5-a reductase in 1, adrenal adenoma in 2, adrenocortical
carcinoma in 2 and in 1 case a testicular Leydig tumor.

Descriptions of selected cases

A 9-year-old boy with von Recklinghausen disease, of short
statue, was referred to the Endocrinology Clinic due to the
advanced symptoms of precocious puberty that, accord-
ing to the mother, persisted for one year. On admission the
following deviations from the normal state were found:
enlarged testes – as in puberty, facial acne, headaches (for
a year), and numerous café-au-lait spots on the skin. Visual
acuity was decreased with concentric narrowing of the
visual field.

Ultrasound examination of the abdomen was normal, tes-
estes of proper echostucture, symmetrical, enlarged, with a
volume of about 12 ml each – as in puberty. The result of a
GnRH test was positive. True, GnRH-dependent precocious
puberty was diagnosed and the boy was referred for CNS
examination.

In MRI examination: pathological mass in the suprasellar
area (Figure 1), 21×17 mm in dimensions, heterogeneously
enhanced following application of gadolinium. The tumor
displaces the pituitary stalk and infundibulum backwards
and to the right and exhibits signs of necrosis in the cen-
tral region. The child was admitted to the Neurosurgery
Department where a stereotactic biopsy was performed –
microscopic examination revealed a benign glial tumor
of 1 grade, of astrocytoma type. Patient’s short stature and
delayed skeletal age were most probably associated with
pressure of the tumor on the infundibulum, which could
have changed its function (decreased growth hormone
levels).

A 6-year-old boy with symptoms of precocious puber-
ty – pubic hair. On admission: right testis was enlarged
and hard. Skeletal age on x-ray examination was 3 years
advanced. Testosterone level was elevated. GnRH test was
negative. GnRH-independent precocious pseudopuberty.

Ultrasound examination (Figure 2): right testis is enlarged
– volume of about 6 ml. In its central region a pathologi-
cal tumor mass of heterogeneous echogenicity and with
considerably increased, abnormal vascular blood flow. The
child underwent surgery. Testis was removed. Histological
examination revealed a benign Leydig cell tumor.

| Age months/years | 18/12–≤3 | 3–4 | 5–6 | 7–8 | 9 | In total |
|------------------|---------|-----|-----|-----|---|---------|
| Girls            | –       | 6   | 7   | 26  | 1 | 39      |
| Boys             | 3       | –   | 6   | 7   | 1 | 17      |

Table 1. Ages of 56 children diagnosed with precocious puberty.

Figure 1. A 9-year-old boy with advanced symptoms of GnRH-dependent
precocious puberty for 1 year, large testes. MRI of the CNS – an abnormal
mass in the suprasellar area, (optic chiasm) heterogeneously enhanced.
Stereotactic biopsy of a tumor – astrocytoma I.
Symptoms of PP regressed after about 6 months. He is under the care of endocrinological outpatient clinic, developing properly; maturation consistent with age.

A 2.5-year-old boy with symptoms of PP: pubic hair, considerable enlargement of the penis and scrotum, darkened skin in this area. Skeletal age was 2 years advanced. Testosterone level was elevated. GnRH test was negative. Low gonadotropin levels. Precocious, GnRH-independent pseudopuberty was diagnosed. Abdominal ultrasound examination (Figure 3): in place of the right adrenal gland there was an abnormal, solid, hypoechogenic, oval, well-demarcated mass, about 28×32 mm in size. Normal testes. CT examination of the abdomen: tumor of the right adrenal gland 29×30×24 mm in size, solid, with density of about 40 HU, heterogeneously enhanced to 140 HU following application of a contrast medium; after 10 minutes the density decreased to 50 HU. Adrenal adenoma was diagnosed. Tumor was removed. Histological examination confirmed the diagnosis of adenoma. PP symptoms regressed.

A 3-year-old patient was admitted to hospital after fainting. Pubic hair was noticed 1 month ago. On admission to hospital: facial acne, pubic hair, enlarged penis, testes not enlarged, a large tumor was palpable in the abdominal cavity. Skeletal age was 2 years advanced. Testosterone level elevated. GnRH test negative. Picture of GnRH-independent precocious pseudopuberty.

Figure 2. A 6-year-old boy with symptoms of gonadotropin-independent PP. Right testis enlarged. US – a heterogeneous mass in the right testis, with significantly increased abnormal vascular flow in the central part. Left testis – normal. Underwent surgery. Histologically: Leydig cell tumor.

Figure 3. A 2.5-years-old boy with gonadotropin-independent PP. Abdominal US (A): an abnormal hypoechoic, oval mass with clear margins in the right adrenal gland. CT (B): a tumor of low density, heterogeneously attenuating after contrast in the right adrenal gland. Histological diagnosis: adrenal adenoma.

Figure 4. A 3-year-old boy with symptoms of gonadotropin-independent PP. US examination (A): a large abdominal tumor, extending from liver to iliac wing, with heterogeneous echostucture, possibly originating from the right adrenal gland or the upper pole of right kidney. Metastases in the liver. CT (B) and MRI examinations confirmed the presence of a large tumor of the adrenal gland. Histological diagnosis: adrenocortical carcinoma.
Ultrasound examination (Figure 4): large tumor of heterogeneous echogenicity filling the right side of the abdominal cavity from the lower margin of the liver to the iliac wing, and crossing the midline. It was difficult to distinguish the tumor mass from the right kidney. Tumor of about 20 cm in size. Metastatic foci in the liver. Testes of about 1.5 ml each, with normal echostructure. CT (Figure 4) and MR imaging confirmed that the tumor derives from the right adrenal gland. CT examination of the chest revealed metastatic foci in both lungs. Infant was treated with cytostatics and underwent surgery, histologically – adrenocortical carcinoma. The child died.

An 18-month-old boy with symptoms of precocious puberty present for 6 months: enlarged penis, pubic hair, testes not enlarged. On admission to hospital: skeletal age advanced by 4 years, level of testosterone significantly elevated, GnRH test negative. GnRH-independent precocious pseudopuberty.

On abdominal ultrasound (Figure 5): a large, spherical, well-demarcated from the surroundings, solid tumor, homogeneous, poorly vascularized, 6.5 cm in diameter, located between the superior pole of the right kidney and the diaphragm. CT examination confirmed the presence of an adrenal tumor. The tumor was surgically removed. Histological examination – adrenocortical carcinoma. Due to the large size of the tumor, the infant underwent a cycle of cytostatic treatment. In the period of 4 years of observation, the child remained in good clinical state, symptoms of precocious puberty regressed. He is developing normally.

Discussion

Precocious puberty (PP) affects about 3% of the population [1]. Girls are affected much more often than boys in a 7:1 ratio [2]. Precocious puberty may be distinguished into two types: central, GnRH-dependent type, in which there is a premature stimulation of the physiological hypothalamic-pituitary-gonadal (HPG) axis, and peripheral, GnRH-independent, not associated with premature oversecretion of gonadotropin-releasing factor and gonadotropin [1–5], iso- and heterosexual. Precocious puberty of the central type is much more common. It constitutes about 80% of all cases [4].

Etiology of the central precocious puberty may be idiopathic when stimulation occurs due to unknown reasons, or
organic, including various types of CNS lesions in the hypothalamic region – tumors of the suprasellar area: hamartomas, gliomas, astrocytomas, extragonadal dysgerminomas, ependymomas, type I neurofibromatosis, tuberous sclerosis as well as other defects and diseases of the CNS, including arachnoid cysts, hydrocephalus [2,3].

True, GnRH-dependent PP in girls is in 80–90% idiopathic, but in boys true PP is idiopathic only in a small percentage of cases. Statistically, CNS pathologies are much more frequent in boys [1–6]. In our material, idiopathic, GnRH-dependent precocious puberty was diagnosed in 36 girls and 5 boys. CNS pathology – brain tumor – astrocytoma was diagnosed in 1 boy with von Recklinghausen disease – type 1 neurofibromatosis (NF1). Patients with NF1 require cautious observation due to a greater propensity to tumor formation [7].

Peripheral, GnRH-independent precocious pseudopuberty is a result of androgenic or estrogenic hormonal stimulation not associated with the activity of the hypothalamo-pituitary-gonadal axis [1–5] and is most often caused by an organic factor, often neoplastic.

This type of maturation may be caused by:
- Tumors releasing LH (luteinizing hormone) or hCG (human chorionic gonadotropin):
  - CNS tumors (teratoma, chorioepithelioma, germinoma)
  - testicular tumors (embryonic carcinoma, germinoma, teratoma),
  - hepatic tumors (hepatoblastoma, hepatoma, teratoma);
- Treatment with human chorionic gonadotropin,
- Adrenal androgenization – congenital adrenal hyperplasia, adrenocortical tumors, hormonally active (adenomas, carcinomas),
- Testicular androgenization: testotoxicosis, testicular Leydig cell tumor (leydigoma, dysgerminoma),
- Androgenization in primary hypothyroidism,
- Use of external sources of androgens.

In our material, peripheral precocious pseudopuberty was diagnosed in 11 boys. Congenital adrenal hyperplasia was diagnosed in 5 boys aged from 5 to 6 years. In all boys skeletal age was advanced by 4–5 years, body proportions were changed – elongated trunk and relatively short limbs. Appearance of tertiary sexual characteristics (pubic hair, enlarged penis, facial acne, voice change) with testes not enlarged, 1–1.4 ml in volume.

In ultrasound and computed tomography examinations, the picture of adrenal glands is usually normal. Among our patients with congenital adrenal hyperplasia (CAH), only in one case an enlarged adrenal gland was identified in US examination. A CT was performed, in which an echogenic structure in the central part of the adrenal gland was identified. This lesion regressed following administration of hydrocortisone. In CAH there is a congenital enzyme block, which leads to high serum levels of adrenal androgens resulting in precocious puberty. Treatment of choice is hormonal replacement aimed at lowering the ACTH level [1,2,4].

Excess of androgens due to overactivity of 5α reductase that was diagnosed in 1 boy from our group is a very rare cause of precocious pseudopuberty. This enzyme metabolizes testosterone to DHT – dihydrotestosterone, the excess of which may cause peripheral androgenization. Treatment with antiandrogens is controversial as these drugs are associated with a serious risk of adverse effects [2].

Adrenal tumors, both adenomas and carcinomas, may occur at every age in both sexes. Hormonally active tumors most commonly secrete androgens leading to the occurrence of symptoms of precocious puberty – in boys homosexual and heterosexual in girls [2]. Feminizing adrenal tumors are less common, reveal themselves before the puberty and cause acceleration of isosexual maturation in girls and feminization, e.g. gynecomastia in boys [2,8].

Ultrasound and CT examinations are of crucial significance for the diagnosis of the tumor, its character and extent.

Adrenal adenoma – well-demarcated in ultrasound examination, solid, most often homogenous and hyperechogenic tumor, round or oval, with smooth borders. In CT examination it is characterized by low density, 10–50 HU, due to high lipid content. It undergoes clear enhancement after contrast agent administration, which quickly diminishes. The treatment method of choice is resection of the tumor.

In the group of treated children, 2 cases of adrenal adenoma were diagnosed in boys aged 2.5 and 5 years with peripheral precocious pseudopuberty (Figure 3). Symptoms of precocious puberty subsided following removal of the tumor.

Adrenocortical carcinoma is a very rare, highly malignant tumor. It constitutes about 0.2% of all neoplasms occurring in children. Most patients (60%) are children below 3 years old [9–11], the second peak occurs in the 5th decade of life.

These tumors may be clinically silent until the moment when clinical symptoms of precocious puberty appear. Virilization predominates among clinical symptoms in children because androgen-secreting cancers occur more often than estrogen-secreting neoplasms. At the time of diagnosis, adrenocortical carcinomas are most often of large sizes and give metastases quickly, which is associated with poor prognosis.

Treatment of choice is surgery and chemotherapy depending on the stage of the tumor assessed in diagnostic imaging – ultrasound, CT examination of the abdomen and chest: stage I – tumor 5 cm or less in diameter, II – tumor larger than 5 cm, does not grow outside the adrenal gland, III – tumor with involvement of regional lymph nodes, IV – distant metastases [12].

At the moment of appearance of clinical symptoms, adrenal carcinomas reach such large sizes that it may be difficult to determine the point of origin and tumor margins in US and CT examinations relative to the adjacent organs. Large cancers have irregular margins, are heterogeneous due to the regressive lesions present inside them – necrosis, bleeding. Solid parts of the tumor exhibit contrast enhancement. Differentiation between benign and malignant adrenal
tumors (with the exception of lipid-filled adrenal adenomas with characteristic appearance in CT) is difficult and often impossible.

Introduction in recent years of a combined PET/CT examination enables simultaneous assessment of anatomy and function of the lesions and, depending on the used radiolabelled substance, allows for better differentiation between benign and malignant lesions, recurrence, tumor spread, distant metastases and monitoring of treatment results [13,14]. It is particularly important in a group of adult patients as common occurrence of clinically silent incidentalomas in the adrenal glands poses a diagnostic problem.

In our population adrenocortical carcinoma was diagnosed in 2 boys aged 1.5 and 3 years. Symptoms of precocious puberty occurred early and were the first manifestations with fast progression. In the three-year-old boy (Figure 4) the neoplastic process was disseminated at the moment of diagnosis. The tumor was very large, of heterogeneous echogenicity on ultrasound examination and heterogeneous density in CT, with areas of necrosis and metastases to the liver and lungs. The infant died despite attempts at chemotherapy and surgical treatment.

In the other boy (Figures 5, 6) the tumor was confined, with smooth margins, did not extend outside the adrenal gland capsule, but due to the size of over 6 cm in diameter chemotherapy was administered in addition to surgery. The child is developing normally and symptoms of PP subsided.

Leydig cell tumor is a rare cause of precocious puberty in boys (1 case in our population, Figure 2). Most often the age of affected boys is less than 6 years. It is a unilateral testicular tumor, solid and well-vascularized on ultrasound examination. Laboratory tests show high serum testosterone concentration. The treatment of choice is removal of the testis together with the tumor. Although Leydig cell tumors are usually benign, metastases were observed after a few years following surgical treatment [2,12,15,16].

Treatment of precocious puberty depends on its etiology. Surgical treatment is recommended in case of tumors, supplied by radio- or chemotherapy in malignancy. Glucocorticoids are administered in congenital adrenal hyperplasia and thyroid hormones in cases of PP caused by hypothyroidism.

If treatment is initiated in the right time, symptoms of precocious puberty subside or regress. Children with central, idiopathic, GnRH-dependent precocious puberty are treated with GnRH analogs.

If not treated at the right moment, precocious puberty initially leads to the acceleration of growth but finally, due to the closure of epiphyseal plates, results in short stature and improper bodily proportions – long trunk and short limbs [2,3,7].

Peripheral precocious puberty occurs less often but it may be caused by dangerous disorders, including neoplasms. Rapid differential diagnosis must be carried out in every case of PP, especially in those appearing in early childhood, characterized by fast course [4,12].

In boys, much more often than in girls, neoplasm is the cause of PP: neoplasm of CNS, adrenal glands, testes. Therefore, early endocrinological diagnostics as well as imaging (US, CT, MRI, PET) and treatment are particularly important for life-saving reasons.

Conclusions

1. Precocious puberty occurs less often in boys, but in our material they comprised 30% of children treated for this disorder.
2. GnRH-independent precocious puberty occurred in 64.7% of boys with PP.
3. Skeletal age was advanced in the studied group by 2–4 years.
4. Adrenal and testicular tumors were the causes of precocious puberty in the youngest group of boys, aged 1.5–6 years.
5. Etiology of PP in boys varies. In every case, the following diagnostic tests should be performed: x-ray assessment of skeletal age, US examination of the testes and abdominal cavity (adrenal glands). In selected cases, abdominal CT and central nervous system MRI should be performed.

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