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Research article

Feminizing Adrenocortical Tumors as a Rare Etiology of Iso/Contrasexual Pseudopuberty

Vuralli D et al. Feminizing Adrenocortical Tumors

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What is already known on this topic?
Feminizing adrenocortical tumors (FATs) are extremely rare tumors that are most commonly seen in men and boys presenting with gynecomastia.While boys present with contrasexual pseudopuberty signs, girls present with isosexual pseudopuberty.

What this study adds?
FATs are more common in children ≤8 years of age, with a median age at diagnosis of 6 years. FATs are usually malignant in adults whereas in children approximately half of the FATs are benign. The assessment of malignant potential depends on clinical behavior of the tumor in children. Although complete surgical resection of benign FATs is thought to be curative, the long-term follow-up is required because of the unpredictability of these tumors. FATs occurring in childhood period may carry a better prognosis than in adult males with most of the FATs in children are followed without recurrence of the tumor since the diagnosis is made in the early period before puberty.

Abstract
Objectives: Estrogen secreting adrenocortical tumors (ACTs) are quite rare, feminizing adrenocortical tumors (FATs) accounting for 0.37–2% of all ACTs. Present study aims to evaluate clinical and hormonal characteristics as well as treatment options and follow-up of FATs in pediatric age group.
Methods: We reviewed medical records of 25 children with ACTs in our unit in last two decades. We reported two new pediatric cases of FAT, one benign and the other malignant, in two genders with different clinical presentations. Literature review revealed 34 pediatric patients (22boys) with FAT among 192 articles identified in pubmed database.
Results: FATs are extremely rare tumors that are most commonly seen in men and boys presenting with gynecomastia. FATs are more common in children ≤8 years of age, with a median age at diagnosis of 6 years. While boys present with contrasexual pseudopuberty signs, girls present with isosexual pseudopuberty. High estrogen level strongly supports diagnosis, while elevations in other adrenal hormones may be seen. FATs are usually malignant in adults whereas in children approximately half are benign. Assessment of malignant potential depends on clinical behavior of tumor in children. Although complete surgical resection of benign FATs is thought to be curative, long-term follow-up is required because of unpredictability of these tumors. Prognosis is generally very poor in adult males. FATs in childhood may carry a better prognosis with most of FATs in children are followed without recurrence of tumor.
Conclusions: FATs are more common in children ≤8 years of age, with a median age at diagnosis of 6 years. FATs in childhood period may carry a better prognosis than in adult males.
Keywords: Adrenal adenoma, adrenal tumor, adrenocortical carcinoma, adrenocortical tumors, childhood, children, children and adolescents, estrogen.

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Introduction
Adrenocortical tumors (ACTs) are rare in childhood, accounting for less than 0.2% of childhood malignancies but nearly 6% of adrenal tumors [1]. Childhood ACTs are usually functional tumors; rate of having hormonal activity in children is 90% compared to 50% in adult cases [2, 3]. While adults usually have a single hormone secretion, children often have mixed hormone secretion. Complete hormonal workup of ACTs revealed the predominance of mixed hormone-secreting type of tumor although some cases lack the appropriate clinical findings. Hormonal work-up of these tumors showed that half of the patient population had tumors secreting a combination of androgens and cortisol, whereas almost one third had ACTs secreting androgens alone [4]. The clinical presentation depends on the hormones secreted from the tumor. The most common presenting symptoms are virilization due to androgen secretion which is, followed by Cushing's syndrome due to

cortisol secretion and then hyperaldosteronism [3-6]. Estrogen secreting ACTs are quite rare, feminizing adrenocortical tumors (FATs) accounting for 0.37–2% of all ACTs [7]. FATs may secrete estrogen (estrone and estradiol) alone or in combination with other adrenal hormones, are more prevalent in adult males, often have malignant behavior and have a poor prognosis [7].

The clinical manifestations of FAT include feminizing symptoms of excessive estrogen production, symptoms of compression of the tumor mass, or constitutional symptoms such as weight loss and fatigue. Girls usually present with precocious puberty (isosexual pseudopuberty), while the boys present with bilateral gynecomastia (contrasexual pseudopuberty) and delayed puberty. In boys gynecomastia is the most common symptom of FAT with a rate of 98% [8]. Diagnosis of FAT depend on the clinical signs and hormonal analysis. Hormone profile shows the overproduction of estrogen alone or in combination with other adrenocortical hormones, alongside normal or low gonadotropin levels [9, 10]. Radiological and histological findings are similar to those of other ACTs. A pathological examination shows positivity with aromatase immune-staining in the tumor tissue [11].

In this study we want to evaluate the clinical and hormonal characteristics as well as treatment options and outcome of the feminizing adrenocortical tumors in pediatric age group. For this purpose we reviewed the medical records of children with an adrenocortical tumor followed in our unit in the last two decades. We planned to evaluate in detail the clinical, hormonal characteristics, treatment methods and outcomes of the patients who were diagnosed with FAT during this period. We also analyzed the features of similar published cases in childhood period through a systematic literature review. By presenting the cases with FAT followed-up in our unit and by reviewing the published cases with FAT in childhood period, we would like to draw attention to this rare tumor and to review the variable characteristics of this tumor in childhood.

Patients and Methods:

The medical records of children with ACT who were followed up between 1999 and 2020 in the pediatric endocrinology unit at Hacettepe University İhsan Dogramaci Children's hospital in Ankara, which is one of the largest tertiary medical centers in Turkey were reviewed retrospectively. Data regarding age, sex, presenting symptoms, clinical characteristics, laboratory investigations including hormonal analysis, imaging techniques (ultrasonography, computed tomography, magnetic resonance imaging), pathology, treatment and outcome were extracted from the medical files. Among all the adrenocortical tumors followed up in our unit, the cases followed with FAT were described in detail. We also performed a literature review including cases with FATs. We performed a search through Pubmed/MEDLINE using the following keywords: “Feminizing adrenocortical tumor’’and “Feminizing adrenal tumor’’and filtered for articles published in English and Turkish. We searched the literature from inception to December 1, 2020. We included all articles that reported children who had feminizing adrenocortical tumors. The following parameters were noted from included studies: age at diagnosis, gender, clinical presentation, hormonal evaluation, treatment options, clinical course of the tumor, survival/follow-up period.

Results

There were a total of 25 patients with ACT followed up in our pediatric endocrinology unit. Since histological criteria to differentiate malignant behavior in childhood ACTS are not reliable, all lesions were categorized as ACT instead of adenoma or carcinoma. According to this classification two patient had FAT and other twenty-three patients had ACT. The clinical, hormonal and pathological characteristics of the cases with ACT are given in a recently written article by Ardicli et al. [12]. Clinical, hormonal, pathological evaluations as well as management and outcome of the patients with FAT are given below in detail.

Case 1

A 13.5-year-old boy presented with bilateral breast enlargement and weight gain for the last four months. No discharge from the breasts was noted. He did not have headache, nausea-vomiting, flushing, palpitation, sweating or diarrhea. He was not using any medication. His family history was unremarkable. On physical examination body weight was 61.4 kg (1.1 SDS), height: 156.4 cm (-0.5 SDS), body mass index: 25.1 kg/m^2 (1.6 SDS), heart rate: 90/min and blood pressure: 140/85 mmHg. He had purple strias, buffalo hump, moon face and centipetal fat accumulation suggesting cushingoid appearance. He had bilateral Tanner stage 4 gynecomastia with a Tanner stage 4 pubic hair, testis volumes of 6/8 ml, and stretch penile length of 7.5 cm. In the laboratory examination he had hyperestrogenism, hyperandrogenism and hypercortisolism (Table 1). Abdominal ultrasonography (USG) showed a 102x94 mm round hypoechoic mass with echogenic septates and increased blood flow at right adrenal lodge. A hypoechoic thrombotic mass markedly occluded lumen of the inferior vena cava (IVC). Abdominal computed tomography (CT) showed the mass had pressure on the right kidney and the right lobe of the liver. A chest CT revealed pulmonary metastasis. Antithrombotic treatment (enoxaparin sodium) was administered for the thrombus in the IVC. Amlodipine was started for hypertension. The mass with right adrenal and tumor thrombus were resected under steroid coverage. The pathological examination confirmed the diagnosis of adrenocortical carcinoma with high mitoses, sinusoidal and venal invasions and penetration of the capsule of the adrenal gland. Hormone levels declined in the postoperative period. The patient was administered a chemotherapy protocol including cisplatin, etoposide and doxorubicin. Hydrocortisone replacement at maintainance dose was given along with mitotane treatment, and the dose was adjusted with respect to the patient's clinical findings. The patient was monitored for blood pressure, serum potassium, plasma renin and aldosterone levels to check for a possible mineralocorticoid deficiency, though no such deficiency was found in the follow up. Thyroid function tests were closely monitored and found normal since thyroid function abnormalities could be observed during mitotane treatment.

While a successful decline was observed in the hormonal secretion and gynecomastia post-surgery, patient developed again gynecomastia and a huge elevation of testosterone, adrenal androgen (androstenedione) and estradiol levels following commencement of mitotane. Since the imaging studies have not shown a relapse or recurrence, elevated testosterone was attributed to the inhibition of 5-α-reductase enzyme activity due to mitotane therapy which was confirmed by elevated T/DHT ratio of 38.5 (testosterone:1374.17 ng/dl, dihidrotestosterone: 357.12 pg/ml) [13]. Serial measurements of testosterone and androstenedione revealed a gradual decline in the hormone levels after the cessation of mitotane treatment. During the follow up of the patient for 3.5 years, he had no clinical symptom and radiological finding indicating recurrence of the tumor.

Case 2

Seven-year-old girl presented with bilateral breast development and appearance of pubic hair lasting for 6 months. She was not using any medication and her family history was unremarkable. On physical examination she had bilateral Tanner stage 3 breast development with a Tanner stage 3 pubic hair. In the laboratory examination she had elevated estradiol and androgen levels with suppressed luteinizing hormone (LH) and the follicle-stimulating hormone (FSH) secretions (Table 1). Abdominal ultrasound showed a 65x53 mm, round hypoechoic heterogeneous mass with clear boundaries at the left adrenal lodge with a uterus of pubertal size and prepubertal sized ovaries. An abdominal CT showed the pressure of mass to the left kidney. The mass with left adrenal was resected and the pathological examination confirmed the diagnosis of adrenocortical tumor. Hormone levels declined in the postoperative period. During the follow up of the patient up to 20 years of age, she had no clinical symptom and radiological finding indicating recurrence of the tumor, having 13 years of disease-free survival.

Literature Review

There were 34 pediatric FAT cases that have been described among 192 articles identified in pubmed database (Table 2). The first pediatric case was a 4.6-year-old male described in 1948 [14]. Twenty-two of the cases (65%) were boys and 12 of them were girls. The age at diagnosis of the cases ranged between 1.5 and 18 years with a median age of 6 years old. The age of diagnosis of two cases was not specified. While the age of diagnosis of 21.9% (7/32) of the remaining 32 cases was <4 years, 65.6% (21/32) of them were 4-8 years old, and 12.5% (4/32) were ≥ 8 years of age at diagnosis. All of 22 boys had bilateral gynecomastia at the time of diagnosis. Penile size enlargement with prepubertal sized testes were other findings seen in boys. In girls, breast development was defined in all cases except two, while vaginal bleeding was associated in a number of 5 cases. Among girls who were not reported to have breast development just virilization was present in one of them [15], and the other case was admitted at the age of 3.7 due to weight loss, irritability, high blood pressure and left abdominal mass was palpated in the physical examination [16]. In addition, abdominal mass was palpated in examination of two boys of 5 and 6 years old and a girl of 6.7 years old [17-19]. Besides virilization findings such as pubic and axillary hair development, and acne formation, accelerated linear growth and advanced bone age were also observed in both genders. Features of Cushing syndrome such as facial edema, strias over the body, hypertension, and delirium were reported in two girls aged 3.7 and 4 years and two boys aged 14 and 18 years [16, 20-22]. There was estrogen secretion alone in eight boys (23.5%, 8/34) aged between 6-8 years. All of the other cases had mixed hormone secretion. While androgen and estrogen secretions were seen together most frequently (%61.8, 21/34), in five cases these secretions were accompanied by excess cortisol (14.7%, 5/34). The mass was surgically removed in all cases. Sixteen of all cases (47.1%) were benign, and twelve of them (35.3 %, 12/34) were malignant according to histological examination. In five of the cases (14.7%, 5/34), histologically benign/malignant distinction could not be made exactly [21, 23-26]. In addition there was a tumor which was first considered benign according to histological examination but later the tumor turned out to be malignant when metastasis occurred [18]. When we add these six tumor cases, the total number of malignant tumors becomes eighteen. The benign vs malign ratio among the patients described in literature is 47% vs 53%. It was stated that mitotane was used in two cases whose pathology was malignant, the other two cases were given chemotherapy, and another two cases received radiotherapy. No other treatment methods were mentioned in the other cases. All sixteen of the patients with histologically benign tumors were alive without recurrence of the tumor between one to fourteen years after surgical excision of the tumors. Fourteen out of eighteen patients with malignant tumors were alive without recurrence of the tumor for varying periods of six months to ten years after removal of the tumors. One of the malignant cases died within sixteen months after disease onset, the other one in the third year, and another died during the operation [15, 20, 27]. A case who was considered to be benign on histological examination was followed up with free of metastasis for 7.5 years, but died 8 years after the operation due to disseminated metastasis [18].

Discussion

Feminizing adrenal tumors are exceedingly rare, accounting for 0.37% of 801 adrenalectomies performed between 1970 and 2003 [7]. They are usually seen in adult males, and are extremely rarely reported in children. Since this tumor is exceedingly rare, cases with FAT have been reported in the literature usually as single case reports [10, 16, 19, 20, 28-40]. The largest published series usually include a maximal of two or three cases [7, 8, 15, 41, 42]. There are two exceptional review studies performed by Gabrilov et al. in 1965 which includes 52 cases reported before 1965 and another by Chentli et al. in 2015 which contains 50 cases reported between 1979 and 2014 [43, 44]. These two reviews are the largest review studies so far, and they mainly involve the adult males. To the best of our knowledge, there is no study that gathers together the pediatric patients with FAT. In this study, we have reported two cases of FAT in childhood period, one benign and the other malignant, in two genders with different clinical presentations. We also performed a systematic literature search (Table 2) and reviewed 34 pediatric patients (22 boys) with FAT. Thus, we specifically emphasized the clinical and hormonal characteristics, as well as treatment options and the follow-up of this rare tumor in pediatric age group.

FATs were more frequent in boys (boy/girl ratio :1.8, 23/13), accounting for nearly two thirds of all pediatric cases. They are more common in younger children with a median age at diagnosis of 6 years (range: 1.5–18). Eighty-five percent of cases is under 8 years old with most between the ages of 4 and 8.The diagnosis of FATs is based on clinical findings and hormonal evaluation, and estrogen secretion is vital. FAT presents with different clinical findings in two genders and two new cases reported in this study delineates the divergence of the presentation of FAT in different genders in children. While boys present with contrasexual pseudopuberty, girls present with isosexual pseudopuberty. All of the boys in literature including our first case, had bilateral gynecomastia which was also painful. Most cases of gynecomastia, including physiological gynecomastia seen during puberty, are caused by an imbalance between estrogen and androgens [45, 46]. Physiological pubertal gynecomastia is most commonly seen in mid-puberty with a Tanner stage 3-4 pubic hair and bilateral testicular volumes of 5-10 mL. Most adolescents during this period have normal estrogen levels, but a few studies have shown high levels in some cases [47-49]. Pathological gynecomastia may rarely be seen in adolescents and prepubertal boys. It is related to conditions where there is absolute or relative estrogen excess. Pathological gynecomastia may be seen in cases of exogenous intake of estrogen-containing drugs, the presence of endogenous estrogen-producing tumors, increased peripheral conversion of androgens to estrogens secondary to increased aromatase activity, androgen deficiency or androgen insensitivity [50]. Gynecomastia presenting at prepubertal age or increasing in size progressively at pubertal age in boys

should be a warning sign for a hormone secreting tumor, especially FAT. In contrast to physiological pubertal gynecomastia in adolescent period, androgen levels inconsistent with the pubertal stage should be taken seriously, and tumors need to be excluded. In girls, the main complaints of FAT were early breast development and/or menstruation. Other signs of precocious puberty such as increased growth velocity and advanced bone age were also observed in both genders. Children also rarely presented with the neurological complications of Cushing syndrome such as delirium and aggressive behavior and signs of high blood pressure [21, 51]. Although it was very rare in childhood, in advanced stages, some patients also presented with abdominal masses or metastases [16, 18, 19].

From a hormonal perspective, FATs secrete estrogen alone or in combination with other adrenocortical hormones (mixed secretions). In adults, estrogen secretion is usually alone, but sometimes overt or subclinical hypercortisolism may accompany, the other hormone secretions such as androgen precursors, aldosterone or inhibin were rarely reported [52, 53]. Among the pediatric patients in literature, mixed secretion was often observed and hyperandrogenism due to secretion of adrenal androgen precursors such as 17-hydroxyprogesterone, deoxycorticosterone, 11-deoxycortisol, androstenedione, dehydroepiandrosterone (DHEA) and DHEA-sulfate were more common than overt or subclinical hypercortisolism. While there was only estrogen secretion in ¼ of the cases in the literature, 60% had estrogen and androgen, and the remaining 15% had cortisol hypersecretion in addition to hyperestrogenism and hyperandrogenism. Two new cases described in this study also had ACT with mixed hormone secretion, in the first case there was a cosecretion of estrogen, cortisol, and androgens whereas in the second case both estrogen and androgen hypersecretion was observed. Contrary to the cases in childhood, adult patients with FAT generally have low testosterone levels attributable to several mechanisms. The first is the hypothalamic inhibition of FSH and LH secretion by estrogen; the second is the inhibition of the Leydig cells by the high estrogen levels, and the third is the increase in sex hormone binding globulin (SHBG) levels secondary to excess estrogen [7, 52]. As SHBG has a high affinity for testosterone, free testosterone levels would fall, leading to findings of hypogonadism [54].

The mechanisms by which FAT cause hyperestrogenism are excessive estrogen production by the tumor, and enhanced conversion of peripheral androgens to estrogen in the adipose tissue [55]. Studies have also shown that FAT produces aromatase mRNA, and an increased aromatase activity has been reported in patients with FAT and shown in vitro [56-58]. Hypogonadotropic hypogonadism due to inhibition of hypothalamus-pituitary-gonadal axis thereby suppressed LH and FSH secretion usually accompany hyperestrogenism [56-58]. This information is important because the gonadotropin level is the only way to differentiate between peripheral, and central precocious puberty as well as normal puberty in children presenting with pubertal findings. In addition, estrogen secretion seen in patients with FAT may remain dependent on pituitary adrenocorticotropic hormone activity and estrogen release from the tumor can be reduced by administering dexamethasone [54].

The main treatment of FATs, like other ACTs, is surgical removal of the tumor. It is recommended that at least 90% of the tumor be excised even in the presence of metastasis [54], as there is a high risk of relapse if not removed. In the literature review, the tumor was tried to be removed by surgical resection in all cases. If the tumor cannot be removed completely by surgery, it is necessary to destroy the remaining tumor and reduce the excess hormones secreted from the tumor. The medical agent frequently used for this purpose is mitotane (ortho paraprime dichloro diphenyl dichloroethane), given its inhibition of hormonal secretion and its cytolytic and adrenolytic properties. Mitotane also induces the formation of free radicals, which in turn inhibit 11-β-hydroxylase and block steroidogenesis [59, 60]. First presented patient in the present study received mitotane and also hydrocortisone 10 mg/m2/d due to mitotane's adrenolytic effect, and was monitored for mineralocorticoid deficiency, although no such findings developed. Mitotane also strongly inhibits 5-α-reductase enzyme activity. This was led an exaggerated elevation of testosterone and its precursors and even estrogen due to aromatization of excessive androgens. This had resulted challenges in the assessment of relapse. Since, the abdominal and thoracal imaging did not reveal any sign of relapse, high level of testosteron, estradiol and androstenedione was attributed to the inhibition of 5-α-reductase enzyme activity. This was confirmed by elevated testosterone/dihydrotestosterone level. Indeed, testosterone and other elevated hormones had gradually declined and reached to the normal values eventually after the cessation of mitotane. This issue should therefore be taken into consideration in case of unexpectedly elevated androgen with no sign of relapse. This inhibition could last for a long time since mitotane is mainly distributed into fat tissue thereby eliminated slowly.

Most of the reported cases of FAT in adult patients are malignant in literature, whereas in children benign FAT were also described in a high number of cases. Approximately half of the FATs in childhood were benign and half were malignant. Actually there are no defined clinical, radiological and even histological criteria other than the behaviour of tumor (recurrence and metastasis) to differentiate benign from malignant, thus the differentiation between adenoma and carcinoma is usually difficult [8, 61]. Although the presence of certain histological predictive criteria involving mitotic activity, atypical mitosis, high nuclear grade, low percentage of clear cells, necrosis, diffuse architecture of tumor, capsular invasion, sinusoidal invasion, and vascular embolism leans more to the diagnosis of carcinoma, the assessment of malignant potential depends on clinical behavior of the tumor in children [8]. In adult tumors histopathological markers such as positivity with aromatase immune-staining can help assessing the malignant potential [11]. There were pediatric cases in literature in whom benign/malignant differentiation of the tumor could not be made or who had tumors first considered to be benign according to the histopathological examination but the tumor turned out to be malignant when metastasis or recurrence detected in the follow-up [18, 23-25]. Therefore some authors have suggested that even in the case of benign histopathological findings, the clinician should be highly suspicious of the benign diagnosis when there is a tumor secreting estrogen [9]. In the first presented case in this report, the patient had metastasis already at the diagnosis of the tumor and FAT in this case was malignant which required medical treatment with mitotane as well as chemotherapy. In the second case presented, there was no metastasis or recurrence of the tumor at the follow-up, total resection of the primary tumor leading to cure and this tumor had a benign course.

Clinical, hormonal, and radiological follow-up after surgical treatment is necessary to detect any metastasis or relapses. As FATs secrete estrogen, postoperative estrogen levels may be used to confirm whether a complete resection of the tumor has been achieved. In the presence of other hormone secretions, the postoperative monitoring of their levels may provide

information on any residual tumor. In both presented patients, as well as in the cases in literature postoperative hormone levels declined. But, as stated above, re-elevation following mitotane therapy perhaps due to inhibition of 5-α-reductase enzyme activity was observed in the first case. It is recommended to check the hormone profile every three months to screen for recurrence. Imaging with a chest and abdomen CT every three months for the first two years, and then every six months for three years, is also recommended in malignant tumors. Annual imaging is recommended after the fifth year [62, 63].
In literature review, all but one of the cases with a histologically classified benign tumor were alive without recurrence of the tumor. Although complete surgical resection of benign feminizing adrenal tumors is thought to be curative, the long-term follow-up is required because of the unpredictability of these lesions. Approximately 75-80% of the malignant cases were alive for a period of 6 months to 10 years after removal of tumor. Five year survival of these tumors could not be given since the follow-up periods of all tumors were uncertain. FAT has a better prognosis in children compared to adults, since the diagnosis is made in the early period before puberty. As with other adrenal tumors, FAT in childhood period tend to occur in prepubertal ages, so excess secretion of adrenal hormones is easily noticed before puberty [4, 64]. Early diagnosis of FAT also is important, as tumor size is associated with prognosis. Although there is not much data in the literature on long-term survival rates of FATs in childhood, they are thought to behave like other adrenocortical carcinomas. In general, the survival rate of adrenocortical carcinomas vary according to tumor stages, and the prognosis changes dramatically in the case of metastatic disease, while 5-year survival rate is 90% in patients with small, totally resectable tumors, it drops to 10% in patients with distant metastases [65]. Mixed hormone secretion, substantially high estradiol levels at baseline and large tumor size are defined as poor prognostic factors in FAT [58]. In the first presented case mixed hormone secretion, elevated basal estradiol level, large tumor size, presence of pulmonary metastasis and thrombus in IVC were criterias for poor prognosis.

Study Limitations

One of the limitations of the study was that it was conducted retrospectively. The number of patients with FAT were also limited due to rarity of this tumor.

Conclusion

Feminizing adrenocortical tumors are extremely rare tumors that are most commonly seen in men and boys presenting with gynecomastia. FATs are more common in children ≤8 years of age, with a median age at diagnosis of 6 years. While boys present with contrasexual pseudopuberty signs, girls present with isosexual pseudopuberty. A high estrogen level strongly supports the diagnosis, while elevations in other adrenal hormones may also been seen. FATs are usually malignant in adults whereas in children approximately half of the FATs are benign. The assessment of malignant potential depends on clinical behavior of the tumor in children. Although complete surgical resection of benign FATs is thought to be curative, the long-term follow-up is required because of the unpredictability of these tumors. For treatment of malignant FATs, mitotane or aromatase inhibitors with or without standard or targeting chemotherapy, in addition to surgical removal, is recommended. The prognosis depends on the stage of the tumor, although it is generally very poor in adult males. FATs occurring in childhood period may carry a better prognosis than in adult males with most of the FATs in children are followed without recurrence of the tumor since the diagnosis is made in the early period before puberty.

Ethics

Ethics Committee Approval: The study was approved by Hacettepe University Ethics Committee (Approval number: GO 20/401)

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Doğuş Vurallı, Nazlı Gönç, Alev Özön, Saniye Ekinci, H.Serkan Doğan, Serdar Tekgül, Ayfer Alikaşifoğlu, Concept: Doğuş Vurallı, Nazlı Gönç, Ayfer Alikaşifoğlu, Design: Doğuş Vurallı, Nazlı Gönç, Ayfer Alikaşifoğlu, Data Collection or Processing: Doğuş Vurallı, Ayfer Alikaşifoğlu, Nazlı Gönç, Alev Özön, Analysis or Interpretation: Doğuş Vurallı, Ayfer Alikaşifoğlu, Nazlı Gönç, Alev Ozon, Literature Search: Doğuş Vurallı, Ayfer Alikaşifoğlu, Nazlı Gönç, Alev Ozon, Writing: Doğuş Vurallı, Ayfer Alikaşifoğlu, Alev Ozon, Nazlı Gönç.

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Table 1. Pre-op and post-op laboratory examinations of the cases					
	Case 1		Case 2		Normal values
Name of the hormone	Pre-op	Post-op	Pre-op	Post-op	
FSH (IU/L)	<0.3	2.94	0.66	4.6	0.7-18
LH (IU/L)	0.27	1.74	<0.2	0.3	2.4-10
Testosterone (ng/dl)	151.01	14.8	116	<20	<20 (prepubertal), 39-631 (Pubertal in boys)
E_2 (pg/mL)	129.37	11.82	275	<20	<10
08.00 ACTH (pg/mL)	<5.0	22.3	19	25	0-46
08.00 Cortisol (µg/dL)	10.47	10.26	6.5	11.6	6.7-22.6
23.00 ACTH (pg/ml)	<5.0				0-30
23.00 Cortisol (µg/dL)	10.2				3-16.6
24 hour urinary cortisol (µg/day)	N/A*				2.6-37
17-OH Progesteron (ng/mL)	5.66	1.11	1.2	0.42	0.59-3.44
11-deoxycortisol (ng/mL)	116.16	4.55	3.4	3.2	<7.2
Androstenedione (ng/mL)	>10.0	0.66	4.1	0.36	<0.51 (prepubertal), 0.31-2.4 (pubertal)
DHEA-SO_4 (µg/dL)	415.26	47.1	>1000	<30	<35 (prepubertal), 35-430 (pubertal)
Na (mEq/L)	139	136	138	140	135-145
K (mEq/L)	4.2	4.3	4.3	4.4	3.4-4.7
Cl (mEq/L)	103	101	105	107	101-109
Renin (pg/mL)	33.2	18.6	28.1	N/A	2.7-16.5 (supine), 5.41-34.53 (standing)
Aldosterone (pg/mL)	77.0	82.4	82.6	N/A	10-160 (supine), 35-300 (standing)
*N/A: Not available					

Table 2. Feminizing adrenocortical tumors in the pediatric age group							
First Author (reference number)	Age (yrs)	Gender	Clinical findings at presentation	Hormonal evaluation (Increased hormone levels)	Treatment	Clinical course of the tumor	Survival/Follow-up
Wilkins [14]	4.7	Boy	Bilateral gynecomastia	Estrogens, 17 ketosteroids	Surgery	Benign	No recurrence in 4 year of follow-up, alive after 14 years
Fontaine [30]	5	Boy	Bilateral gynecomastia	Estrogens, 17 ketosteroids	Surgery	Malignant with vascular spread	No recurrence 7 years later, alive after 10 years
Snaith [25]	5.5	Girl	Breast development, pubic hair, vaginal bleeding	Urinary estrone, estradiol, estriol, 17 ketosteroids	Surgery	Anaplastic changes (malignant?)	Alive and well after 8 years
Mosier and Goodwin [31]	7	Boy	Gynecomastia, accelerated linear growth	Estrogens, 17 ketosteroids	Surgery	Benign	2 year follow-up, no recurrence, alive after 4 years

Peluffo [17]	6.7	Girl	Breast development, axillary and pubic hair, vaginal bleeding, painful abdominal mass	N/A	Surgery	Malignant	N/A
Ferrante [66]	2.2	Girl	Breast enlargement, pubic hair, hypertrophy of labia minora, advanced bone age	N/A	Surgery	Malignant	N/A
Wilkins [67]	3	Girl	Vaginal bleeding, breast development, accelerated bone age, pubic hair	Estrogens, 17 ketosteroids in 24 hour urine	Surgery	Benign	3 years no recurrence
Bacon and Lowrey [18]	6	Boy	Gynecomastia; acne, pubic hair Palpable tumor	Estrogens, 17- ketosteroids	Surgery	Originally benign, at follow up malignant (adenoma with neoplastic thrombus)	He was alive, well and free of metastases for 7 and a half years, then died of disseminated metastasis 8 yrs after operation; 9 yrs. after disease onset.
Halmi [20]	4	Girl	Signs of virilization, hypercortisolism, hyperestrogenism	Urinary 17-ketosteroids, 17-hydroxycorticoids. Urinary DHEA	Surgery op'DDD	Malignant	Recurrence of tumor and metastases to lungs and liver Died 3 years after the onset of disease
Castleman [27]	6.8	Boy	Gynecomastia, pubic and axillary hair deveopment, grow rapidly	Elevated urinary 17-ketosteroid	Surgery	Malignant with pulmonary metastases	Died on operating table
Leditschke [19]	5	Boy	Bilateral gynaecomastia (no pain, no discharge from the nipples), advanced bone age, increased appetite, pubic and axillary hair development, palpable tumor	Elevated urinary 17-ketosteroid and 17hydroxyketosteroid, and urinary estrogens	Surgery	Benign (From the pathological evidence it was unable to predict how the tumor will behave)	No recurrence 1 year postexcision
Bhettay [10]	6	Boy	Bilateral gynecomastia	Urinary estrogens	Surgery	Benign	3 years later no signs of recurrence
Howard [32]	N/A	Boy	Bilateral gynecomastia	Elevated estrogen levels but normal levels of 17-ketosteroids.	Surgery	Benign	N/A
Visconti [16]	3.7	Girl	Left abdominal mass, weight loss, irritability, high blood pressure	24 hour urinary 17-hydroxy- and 21-oxosteroids	Surgery, Chemotherapy	Malignant	No recuurences in 39 months
Sultan [33]	15	Boy	Bilateral gynecomastia,prepubertal sized testes, pubic hair was present	Estradiol (urine and plasma) urinary 17-hydroxysteroids slightly increased	Surgery	Benign	2 year follow-up no recurrence
Wohltmann [24]	1.8	Girl	Breast development, clitoral enlargement, and an estrogenized vagina, pubic hair	Estradiol, DHEA-SO4	Surgery	Capsular invasion (malignant?)	Patient is healthy over 10 years later

Drop [34]	6.5	Girl	Breast development, pubic and axillary hair	Estradiol, testosterone, 11 deoxycortisol, 17-OH-progesterone, DHEA, DHEA-SO4, androstenedione	Surgery, Radiotherapy	Malignant	No recuurence after 1 year
Itami [35]	6	Boy	Bilateral gynecomastia, axillary and pubic hair, penile size enlargement	Estrone, estradiol, testosterone, androstenedione, 11-deoxycortisol	Surgery	Benign	N/A
Comite [23]	2.8	Girl	Breast and pubic hair development	Estradiol, estrone, DHEA, DHEA-SO4, androsteneione, testosterone	Surgery	Potentially malignant (Extension of the tumor into the capsule)	No recurrence 1 year after surgery
Telander [36]	N/A	Boy	Bilateral gynecomastia	Estradiol	Surgery	Benign	N/A
Desai [42]	8	Boy	Bilateral gynecomastia	Estradiol	Surgery	Benign	N/A
Mc Kenna [15]	6	Girl	Virilization	Estradiol, DHEA-SO4, testosterone, androstenedione	Surgery	Malignant	Recurrence and died 16 months after presentation
Bass [37]	7	Boy	Bilateral gynecomastia, and rapid growth over the preceding six months	Estradiol elevated DHEAS, androstenedione, 11-deoxycortisol mildly increased	Surgery	Benign	No recurrence in 6 months
Ghazi [21]	14	Boy	Gynecomastia, facial edema, stria, hypertension, delirium, features of Cushing syndrome	Estrogen, Cortisol, 24 hour urinary 17-hydroxysteroids	Surgery Bilateral mastectomy	Malignant? (tumor> 100 gr and 6 cm in size)	No recurrence after one year
Watanabe [38]	1.5	Boy	Bilateral gynecomastia, pubic hair, penile size enlargement	Estradiol, testosterone DHEAS	Surgery, mitotane	Malignant	No recurrence in 6 months
Phornphutkul [57]	7.8	Girl	Isosexual precocious puberty, breast development at 7.75 years old, menarche at 8.75 years old, pubic hair development	Estradiol, estrone, DHEA-S, increased 17-ketosteroids, estrone, estradiol, and estriol in 24 hour urine analysis, No suppression in cortisol levels in dexamethasone suppression tests	Surgery	Benign	No residue or recurrence in the first year following surgery
Hsiao [29]	2.2	Boy	Bilateral gynecomastia, pubic hair development	Estradiol, testosterone	Surgery	Benign	5 years later no recurrence
Bouyahia [28]	5	Girl	Isosexual precocious puberty (breast development, menarche, pubic hair deveopment	Estradiol, testosterone	Surgery	Benign	After a follow-up of 6 years, our patient has not had any relapse or metastasis.

Bawri [22]	18	Boy	Bilateral gynecomastia, striae over axilla, and breast, thigh, and facial puffiness for 4 years, Cushingoid appearance Dull, vague abdominal pain localized to the right upper quadrant	Cortisol, DHEA-SO4	Surgery	Malignant	The patient is alive with no metastases 1 year after the surg
Sindgikar [39]	6	Boy	Bilateral gynecomastia	Estradiol	Surgery, chemotherapy (cisplatin, etoposide)	Malignant with micrometastasis	N/A
Angotti [26]	7	Boy	Bilateral gynecomastia, increased somatic growth	Estradiol	Surgery	Low risk of malignancy	N/A (1 month following surgery patient was well)
Soliman [68]	6	Boy	Bilateral gynecomastia and breast tenderness	Estradiol	Surgery	Benign	N/A
Guidoni [69]	7.5	Boy	Bilateral gynecomastia	Estradiol	Surgery	Benign	No recurrence after 1 year
Takeuchi [40]	4.7	Boy	Bilateral gynecomastia, growth spurt, no sign of virilization	Low LH/ FSH levels and elevated estradiol/testosterone levels, Elevated estradiol, testosterone, DHEA-SO4, androstenedione high percentage of urinary estrogen metabolites	Surgery	Malignant	No relapse after 2 years An investigation for *TP53* gene aberrations revealed the presence of a germline point mutation in exon 4 (c.215C>G (p.Pro72Arg))
Presented patients in this report	13.5 7	Boy Girl	Bilateral gynecomastia, cushingoid appearance, hypertension Breast development, vaginal bleeding	Estradiol, androgens, cortisol Estradiol, DHEA-SO_4	Surgery Surgery	Malignant (metastatic) Benign	Alive with no recurrence for 3.5 years Alive with no recurrence for 13 years