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Case Report

Non-hormonal Clitoromegaly due to Clitoral Priapism Caused by Appendicitis/Appendectomy

Gurpinar Tosun et al. Non-hormonal Clitoromegaly

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What is already known on this topic?
- Clitoromegaly is usually caused by hyperandrogenism
- There are rare non-hormonal etiologies of clitoromegaly
- Penile priapism can be related to appendicitis

What this study adds?
This unique case illustrates that;
- Prolonged clitoral priapism can present with clitoromegaly in children
- Clitoral priapism can also be related to appendicitis/appendectomy
- Pseudoephedrine treatment is helpful in clitoral priapism

Abstract
Clitoromegaly usually develops due to hyperandrogenism. There are few cases of clitoromegaly described without clinical and biochemical hyperandrogenism. Clitoromegaly due to clitoral priapism and clitoral priapism after appendectomy have not been reported previously. A 7-year-old girl was referred for enlargement of the clitoris. She expressed having a mild, pulsating clitoral pain starting three days after an appendectomy operation. Subsequently, painful swelling and an increase in the size of the clitoris was observed. Her growth and physical examination were normal other than a clitoromegaly. The conditions related to androgen excess were excluded by comprehensive work-up. The color Doppler ultrasound revealed a high peak systolic velocity and resistance in the cavernosal artery consistent with clitoral priapism. The patient's complaints improved significantly with oral pseudoephedrine and intracavernosal aspiration. This unique case shows that clitoral priapism is a rare non-hormonal cause of clitoromegaly and can occur after appendectomy. Pseudoephedrine treatment is helpful in alleviating the symptoms.
Keywords: Non-hormonal clitoromegaly, clitoral priapism, clitorism, acute appendicitis, pelvic inflammation, pseudoephedrine

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Introduction
Clitoromegaly is an abnormal enlargement of the clitoris and mostly due to androgen excess (1). However, a few case reports have described clitoromegaly without hyperandrogenism, including neurofibromatosis, epidermoid cysts, other tumors and syndromes such as Fraser, Donohue, Seckel and Apert Syndrome (1-6).
Clitoral priapism is a rare condition that is characterized by a prolonged, painful erection of the clitoris which is not associated with sexual arousal (7). Engorgement of the clitoris and the surrounding tissues with accompanying pain is the typical presenting symptom.
In children, penile priapism usually occurs in the setting of sickle cell anemia or leukemia (8, 9). Other conditions associated with priapism include local malignancies, certain medications, hematologic and thromboembolic disorders, and neurologic conditions such as transverse myelitis (8). Pelvic inflammation caused by appendicitis, can lead to the irritation of the nervi erigentes or pelvic plexus causing a neurogenic priapism (9). The association of acute appendicitis and priapism is limited to six male cases reported in the literature (8-11).
Herein, we report our experience with a seven-year-old girl who was referred to a pediatric endocrinology unit due to clitoromegaly and was diagnosed to be the first case of clitoral priapism associated with appendicitis.

Case Report
A 7-year-old girl presented with a progressive, painful swelling of the clitoris that had worsened for the last two weeks. The symptoms started 3 months ago when she had acute appendicitis and an appendectomy operation. She expressed a mild, pulsating pain which was aggravating just before voiding and decreasing thereafter. In the last two weeks, she had multiple

emergency visits for a stabbing pain in her vulva and a gradual increase in the size of her clitoris. She had no previous illness, no recent history of trauma, medication use or infection. There was no family history for sickle cell anemia or cancer.
The physical examination was unremarkable except the clitoris, which was stimulated and tender. Clitoris was enlarged and measured at 2.4 cm for length and 1.2 cm for width (Normal<1.0 cm) **(Figure 1a)**. The urethral and vaginal orifices were normal. She had no evidence of posterior fusion. Her pubic hair and breast development were consistent with Tanner stage I. Her growth was not accelerated (height 118.4 cm, -0.9 SDS; weight 22.4 kg, -0.4 SDS). There was no other clinical evidence of hyperandrogenism including acne, oily skin, body odor or temporal balding.
A complete blood count (CBC), sedimentation rate and PT/PTT were normal. Hemoglobin (Hb) electrophoresis and urinalysis was normal. There was no evidence of androgen excess in biochemical evaluation (**Table 1).** Pelvic ultrasound was normal. Karyotype analysis was reported 46, XX.
The color Doppler ultrasound revealed a high resistance flow in the cavernosal artery with a decreased venous flow consistent with clitoral priapism. The cavernosal artery resistive index was 0.86 and peak systolic velocity was 32.9 cm/sec **(Figure 1b)**.
The patient was started on oral pseudoephedrine (Sudafed®) 15 mg/every 8 hours. In the following 72 hours, the clitoral swelling was reduced, and the pain that was associated with urination only happened once when the pseudoephedrine dose was skipped. The dose of pseudoephedrine was increased to 30 mg every 8 hours after the first week of treatment. However, the patient developed tachycardia 3 weeks after the initiation of treatment which led to discontinuation of pseudoephedrine. Oral ibuprofen (~15 mg/kg/day, every 8 hours) treatment was then initiated due to pain associated with clitoral priapism.
Due to persistence of the symptoms, intracavernosal needle aspiration and cystoscopy were performed. There was no sign of ischemia or acidosis in the blood gas analysis of cavernosal blood (pH=7.52, PCO_2=27 mmHg, PO_2=219 mmHg). Subcutaneous injection of 0.5 mL 0.25% bupivacaine around the clitoris was performed for local anaesthesia with only limited decrease in clitoral pain. Cystoscopy was performed to rule out urologic problems which might be related to priapism revealed only a mild trabeculation in the bladder. DMSA (Tc-dimercaptosuccinic acid) scintigraphy and uroflowmetry were normal. Oral ibuprofen treatment was continued. One week after cystoscopy, oral pseudoephedrine 15 mg every 8 hours treatment was resumed because of persistent priapism. There was a significant improvement in the patient's complaints after restarting pseudoephedrine. She reported no pain or swelling but urgency before voiding. The clitoris size was regressed to 1.9 cm **(Figure 1c)**. The color Doppler ultrasound was repeated at the end of a month of regular pseudoephedrine treatment which showed normal peak systolic velocity in the cavernosal artery (18.8 cm/sec) with lower resistance flow (resistive index: 0.66) **(Figure 1d)**. She remained on the pseudoephedrine treatment for another three months with reportedly less frequent and milder pain usually before voiding. Follow-up at 6 months after diagnosis, the family reported rare and mild episodes of priapism despite discontinuation of pseudoephedrine. There was no further decrease in the clitoral size.

Discussion

Clitoromegaly is generally associated with androgen excess conditions such as virilizing forms of congenital adrenal hyperplasia, virilising adrenal and gonadal tumors. Exhaustive hormonal work-up and the absence of other signs of hyperandrogenism in the present case excluded androgen excess. Priapism of the clitoris is a rare condition associated with prolonged erection of the clitoris causing engorgement, swelling, and pain to the clitoris and immediate adjacent area. Prolonged penile priapism is known to cause penile enlargement (12). Although not reported previously, we believe that clitoral priapism in our case caused clitoral enlargement similar to that in males. All of the patients with clitoral priapism reported so far were adults and the typical initial symptoms are vulvar and clitoral pain with swelling and tenderness (13-19). Most reported cases of clitoral priapism were drug-induced, all having alpha-adrenergic blocking potential. The most commonly reported drug was trazodone. (14, 16, 17).
Present case represents the first prepubertal case of clitoral priapism in whom clitoromegaly was a presenting symptom and also the first clitoral priapism observed after appendicitis/appendectomy, a known etiology for penile priapism.
The main physiologic mechanism of priapism consists of impaired outflow from the corpora cavernosa through direct venous obstruction or failure of the alpha-adrenergic relaxation system resulting in prolonged relaxation of corporal smooth muscle (17, 20). There are three types of priapism: ischaemic (low-flow or veno-occlusive) (LFP), stuttering (intermittent or recurrent) and non-ischaemic (high-flow) (20). The high-flow type characterised by an increase of arterial inflow, does not appear to be a factor in women (7, 16, 17). LFP occurs because of venous outflow obstruction usually seen in the setting of sickle cell anemia or leukemia in children (20). Inflammation is an uncommon etiology of LFP. It has been reported in systemic infections such as mumps, Rocky Mountain spotted fever, tularemia, undulant fever, Mycoplasma pneumoniae, Coxsackie B and echovirus 14 (8, 10, 21-23). Appendicitis, Crohn's disease, ulcerative colitis and localized urogenital infections such as chronic prostatitis and urethritis can cause pelvic inflammation that can lead to irritation the nervi erigentes or pelvic plexus causing a neurogenic LFP (9, 24, 25). There are six reported cases of LFP associated with appendicitis appearing in the literature to date and all of them are males (9). In three of the reported cases, priapism was the main complaint leading to the diagnosis of appendicitis and in the other three cases priapism was developed as a postoperative complication (8-11, 26, 27) similar to seen in our patient.
The intermittent nature of the symptoms and shorter, self-limiting episodes of clitoral priapism in our patient were consistent with stuttering priapism that has similar etiology with LFP. Sickle cell anemia is the most common cause of stuttering priapism (28). However, priapism secondary to sickle cell anemia has not been reported in females. Furthermore, Hb electrophoresis in our patient was normal. Although the underlying mechanism of stuttering priapism is still unknown, it is thought that neurogenic or endothelial dysregulation of smooth muscle relaxation is involved in the pathophysiology of this condition (20, 28). In this context, therapeutic agents that help detumescence of erectile tissue by increasing the smooth muscle tone of the corpus cavernosum can be used in the treatment.
Pseudoephedrine that is more commonly used as an oral decongestant, is often used as a first-line treatment for stuttering priapism (28). Pseudoephedrine acts on two receptors in bronchial smooth muscle to induce relaxation through cAMP and vasoconstriction via α-adrenergic receptors in the respiratory mucosa. Although smooth muscle contraction is possibly mediated by the effects of pseudoephedrine on α-adrenergic receptors, its effects on smooth muscle have not yet been

studied. In studies conducted in a small number of cases in stuttering priapism due to sickle cell anemia, a variable response to prophylactic treatment with pseudoephedrine has been observed (29, 30).

Intracavernosal injections to cavernosaphenous shunts had been performed in other reported cases with appendicitis related LFP (8-11). Intracavernosal needle aspiration, and local anaesthesia with bupivacaine, resulted in partial benefit in our patient. Unlike appendicitis associated with LFP and other cases of LFP, cavernosal blood gas analysis did not suggest ischemia or acidosis. In the literature, there is no case in which clitoral cavernosal blood gas analysis was performed. Pseudoephedrine treatment, which has been shown to work in cases of stuttering pediatric male priapism (29) and in one case of persistent symptomatic female priapism (17) was also successful in our case. Besides the significant decrease in patient's complaints and clitoral size, we were able to objectively demonstrate a significant decrease in the cavernosal artery resistive index compared to pre-treatment measurement by Doppler ultrasound imaging.

In conclusion, clitoral priapism should be kept in mind as a rare non-hormonal cause of clitoromegaly. Priapism associated with acute appendicitis can also occur in females. Oral pseudoephedrine treatment is helpful in alleviating the symptoms.

Statement of Ethics

The parents gave their written informed consent to publish the data and pictures of the patient.

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Figure 1. Non-hormonal clitoromegaly due to clitoral priapism. (a) The appearance of the clitoris before treatment. **(b)** The color Doppler ultrasound imaging of cavernosal arterial peak systolic velocity (32.9 cm/sec) and cavernosal arterial resistive index (0.86) before treatment. **(c)** The appearance of the clitoris after treatment. **(d)** The cavernosal arterial peak systolic velocity (18.8 cm/sec) with low resistive index (0.66) after the treatment of clitoral priapism. (The imaging studies of clitoral vascularization are lacking in the literature. Although the normal values of the clitoral cavernosal arterial resistive index are not known, the decrease seen after the pseudoephedrine treatment was apparent and parallel the clinical response

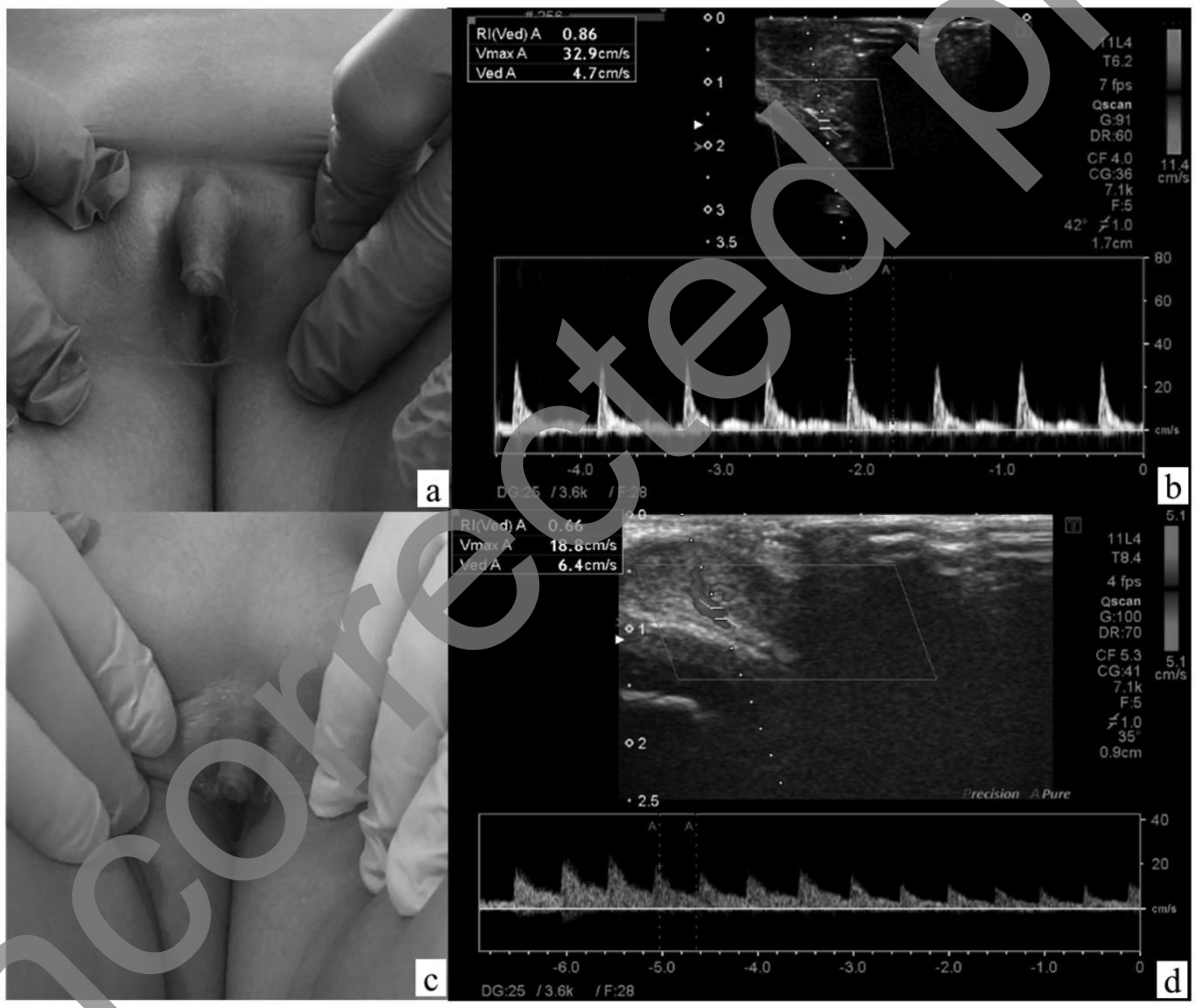

Table 1. Laboratory findings of the patient at presentation.

	Levels	Reference values
Total testosterone*	0.05 μg/L	(0.00-0.20)
DHEA*	0.4 μg/L	(0-3.4)
DHEAS*	155 μg/L	(440-3320)
Δ4-androstenedione*	0.17 μg/L	(0.06-1.15)
17OHP*	0.29 μg/L	(0.00-0.90)
21-deoxycortisol*	< 0.24 μg/L	(0.06-0.51)
11-deoxycortisol*	0.63 μg/L	(0.00-3.44)
FSH	3.16 U/L	(1.0-4.2)
LH	< 0.2 U/L	(0.02-0.3)
E2	< 5 ng/L	(< 15)
AMH	2.51 ng/mL	(0-8.8)
AFP	0.49 U/mL	(0.49-9.84)
HCG	< 0.5 U/L	(< 5)

*Assay method is liquid chromatography mass spectrometry
DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone-sulfate; 17OHP, 17α-hydroxyprogesterone; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol; AMH, anti-mullerian hormone; AFP, alpha fetoprotein; HCG, human chorionic gonadotropin. Conversion factors for SI units are: E2, ×3.67 pmol/L; DHEAS, ×2.71 nmol/L; DHEA, ×3.44 nmol/L; Δ4-androstenedione, ×3.49 nmol/L; total testosterone, ×3.47 nmol/L; 17OHP, ×3.02 nmol/L.