Review Article

Sexual Development

Sex Dev 2018;12:163–174
DOI: 10.1159/000489385

Accepted: November 28, 2017
by M. Schmid
Published online: May 26, 2018

Clitoromegaly in Childhood and Adolescence: Behind One Clinical Sign, a Clinical Sea

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Keywords
Adolescence · Childhood · Clitoromegaly · Hyperandrogenism · Sexual disorder

Abstract
The clitoris is a highly complex organ whose structure has only been clarified in recent years through the use of modern imaging techniques. Clitoromegaly is an abnormal enlargement of this organ. It may be congenital or acquired and is usually due to an excess of androgens in fetal life, infancy, or adolescence. Obvious clitoromegaly in individuals with ambiguous genitalia is easily identifiable, whereas borderline conditions can pass unnoticed. Case reports of clitoromegaly with or without clinical or biochemical hyperandrogenism are quite numerous. In these subjects, a comprehensive physical examination and an accurate personal and family history are needed to investigate the enlargement. We reviewed the literature on the conditions that may be involved in the development of clitoromegaly in childhood and adolescence.

Clitoromegaly (or macroclitoris) is an abnormal enlargement of the clitoris. It is congenital or acquired, most often as a result of exposure to an excess of androgens in fetal life, infancy, or adolescence. Whereas obvious clitoromegaly in subjects with ambiguous genitalia is easily identifiable, borderline conditions can pass unnoticed. In individuals with hypertrichosis, the most common sign of hyperandrogenism, clitoromegaly should be recognized and interpreted as a mark of an underlying disease.

Anatomy, Embryology, Physiology

The clitoris is a highly complex organ whose structure has only really been clarified in recent years through the use of modern imaging techniques [O'Connell et al., 2005; Foldès and Buisson, 2009]. Clinically, most of the organ is hidden by the skin and connective tissue of the vulva. The clitoris comprises an external portion made up of the glans and hood and an internal body consisting of the root, crura, and bulbs [Verkauf et al., 1992]. In the 4th week of fetal life, the genital tubercle forms from mesenchymal proliferation, and a protophallus begins to develop ventral to the cloacal membrane. The genital tubercle becomes the clitoris, which is recognizable by the 14th week [Schünke et al., 2014]. Embryologically, the clitoris is homologous to the male penis. In the absence of testosterone produced by the gonads, the wolffian ducts regress and the müllerian ducts differentiate into the fallopian tubes, the uterus, and the upper third of the vagina. As a consequence, 5α-reductase type 2, which is localized in the genital ridge, lacks the sub-

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Table 1. Dimensional criteria of clitoromegaly in time

Authors	Measurements
Dickinson, 1949	crosswise width >4 mm, lengthwise width >5 mm
Puppo [2011]	CI >35 mm^2
Oberfield et al. [1989]	lengthwise width >6 mm, crosswise width >4 mm
Sane and Pescovitz [1992]	lengthwise width >5 mm, crosswise width >3 mm, CI in newborn >13.3 mm^2 CI in childhood >16.7 mm^2 CI in adolescent >20.7 mm^2
Kessler [1998]	introduction of phallometer, lengthwise width >9 mm
Brodie et al. [2016]	length of hood: 0–3 years >12.6 mm 4–8 years >18.8 mm 9–12 years >24.2 mm 13–16 years >27.4 mm; crosswise width: 0–3 years >5 mm 4–8 years >6 mm 9–12 years >5 mm 13–16 years >8 mm

CI, Clitoral index = lengthwise × crosswise widths.

strate to form dihydrotestosterone [Lee, 2004]. The lack of fusion of the labioscrotal folds finally leads to formation of open labia, a perineal vaginal orifice, and a perineal urethra. Although the prenatal female internal and external genital development appears to be a passive process, the tissues of the female fetus are capable of responding to testosterone [Rhen and Cidlowski, 2004].

Clitoral Size

Whereas reference data for the size of the clitoris are available in adult women, a reliable definition of clitoromegaly in children is based on a limited number of studies. Dickinson's Atlas of Human Sex Anatomy [Dickinson, 1949] reports the width and length of the normal clitoris. The clitoral index (CI), the product of lengthwise and crosswise widths, was introduced in the gynecological and obstetrical terminology in 1980 [Puppo, 2011]. In 1998, a phallometer was used for the first time to measure the size of the clitoris in infants [Kessler, 1998]. Since then, measurements have been performed in infants, children, and adolescents [Oberfield et al., 1989; Sane and Pescovitz, 1992] (Table 1). In a recent study, Brodie and co-workers [2016] have measured the external genitalia of 58 pediatric patients of different ages. Based on these data, clitoromegaly is diagnosed when the crosswise width of the glans is >5 mm between 0–3 years, >6 mm between 4–8 years, >5 mm between 9–12 years, and >8 mm between 13–16 years; when its lengthwise width is >5–6 mm; and when the length of the hood is >12.6 mm between 0–3 years, >18.8 mm between 4–8 years, >24.2 mm between 9–12 years, and >27.4 mm between 13–16 years. However, further data are required to improve the CI (Fig. 1).

Pathological Conditions

Whereas clitoromegaly is seen in several congenital conditions, an acquired enlargement is uncommon. Several case reports have described clitoromegaly with or without clinical or biochemical hyperandrogenism, and a variety of factors may be involved. An accurate physical examination and a detailed personal and family history are required to investigate the enlargement. Clitoromegaly is usually classified according to Copcu and co-workers [2004] as nonhormonal, hormonal, pseudo-clitoromegaly, and idiopathic (Fig. 2; Table 2).

Disorders of Sex Development

Disorders of sex development (DSDs) are congenital conditions involving an atypical development of chromosomal, gonadal, or anatomical sex and more or less ambiguous genitalia at birth [Hughes et al., 2006]. Since clitoromegaly is part of a complex disorder, the isolated condition is relatively unusual in intersex patients. Advances in molecular genetics have led to a revision of the classification and nomenclature of DSDs. This study adopts the division into 46,XX DSDs, 46,XY DSDs, and sex chromosome DSDs according to the Chicago Consensus of 2005 and reviews the conditions where clitoromegaly may be the only sign of the DSD.

46,XX DSDs: Disorders of Hormone Synthesis or Action

Among 46,XX DSDs, congenital adrenal hyperplasia (CAH) is the most common hormonal cause of virilization of the external genitalia due to an enzyme defect in the steroid biosynthesis pathway. The estimated prevalence of CAH is 1/10,000, and its annual incidence ranges from 1/5,000 to 1/15,000. In most cases, CAH is caused by a mutation in the *CYP21A2* gene (chromosome 6p21.3), which encodes an enzyme that controls cortisol and aldosterone production [Speiser et al., 2010]. Consequently, replace-

Table 2. Etiological classification

Hormonal condition	Nonhormonal condition	Pseudoclitoromegaly	Idiopathic
Endocrinopathies	neurofibromatosis		
Masculinizing tumor	epidermoid cysts		
Exposure to androgens	other tumors		
Syndromes with virilization	syndromes without virilization		
	nevus		

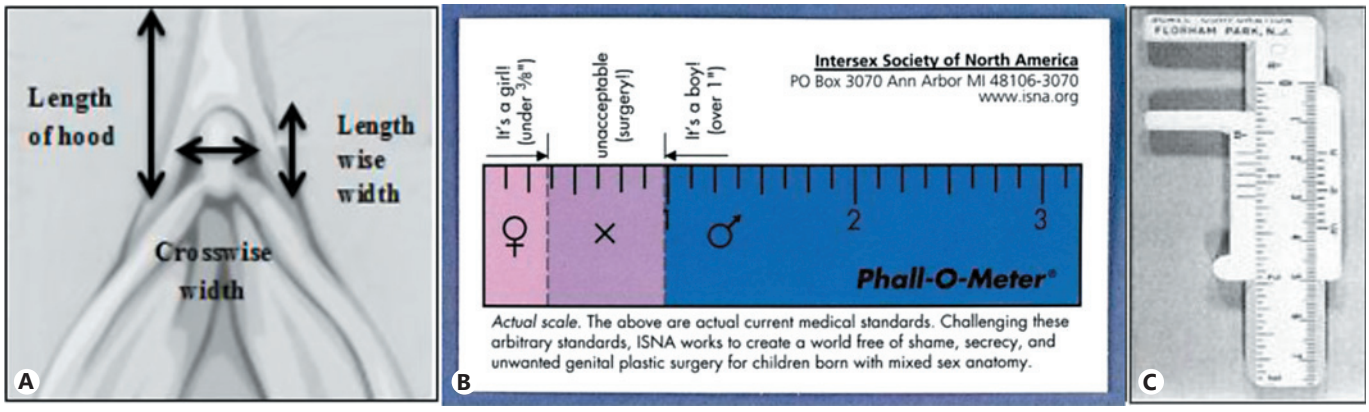

Fig. 1. A Clitoral meeasurements. **B** Phall-O-meter of the Intersex Society of North America. **C** Phallometer.

ment treatment with cortisol or aldosterone reduces the excess adrenocorticotropic hormone, hence androgen overproduction by the adrenal gland. CAH is divided into a classic form, characterized by salt-wasting and/or simple virilization, and late-onset or non-classic CAH (NCCAH), where isolated clitoromegaly is more frequent. Fetal exposure to abnormal androgen levels causes masculinization of female genitalia, with a spectrum of abnormalities that include clitoromegaly [Bachelot et al., 2017]. Isolated clitoromegaly has been described both in CAH and NCCAH [Siddiqui et al., 2013; Moura-Massari et al., 2016].

Rare enzyme defects, like 17α-hydroxylase deficiency, may be seen at puberty in patients with clitoromegaly due to peripheral conversion of testosterone [George et al., 2010].

Other female 46,XX DSDs include disorders of gonadal development, such as 46,XX testicular and 46,XX ovotesticular DSD (Table 3).

46,XY DSDs: Disorders of Androgen Synthesis or Action

Disorders of androgen action are the main cause of male pseudo-hermaphroditism. Patients have female genitalia with different degrees of masculinization, clitoromegaly, and abnormalities that may include a severely bifid scrotum. These disorders encompass 5α-reductase deficiency and androgen receptor defects and are divided into complete and partial androgen insensitivity. The latter syndrome covers a wide spectrum of undervirilization phenotypes including clitoromegaly (Table 4).

Sex Chromosome DSDs

Sex chromosome DSDs include 45,X Turner syndrome and its variants, 47,XXY Klinefelter syndrome and its variants, 45,X/46,XY mixed gonadal dysgenesis, and chromosomal ovotesticular DSD (46,XX/46,XY chimeric or mosaic type). These DSDs derive from numerical sex chromosome abnormalities that lead to abnormal gonad development and dysgenesis of testicular and streak gonads [Jung et al., 2015]. Klinefelter and Turner syndrome are the most common sex chromosome abnormalities. Patients with 45,X/46,XY mixed gonadal dysgenesis show a range of clinical manifestations, including partial virilization and ambiguous genitalia at birth, or have a completely male or female phenotype. In chromosomal ovotesticular DSD (chimeric or mosaic type), ovarian and testicular tissue is found in the same or the opposite gonad, similar to patients with 46,XX and 46,XY ovotesticu-

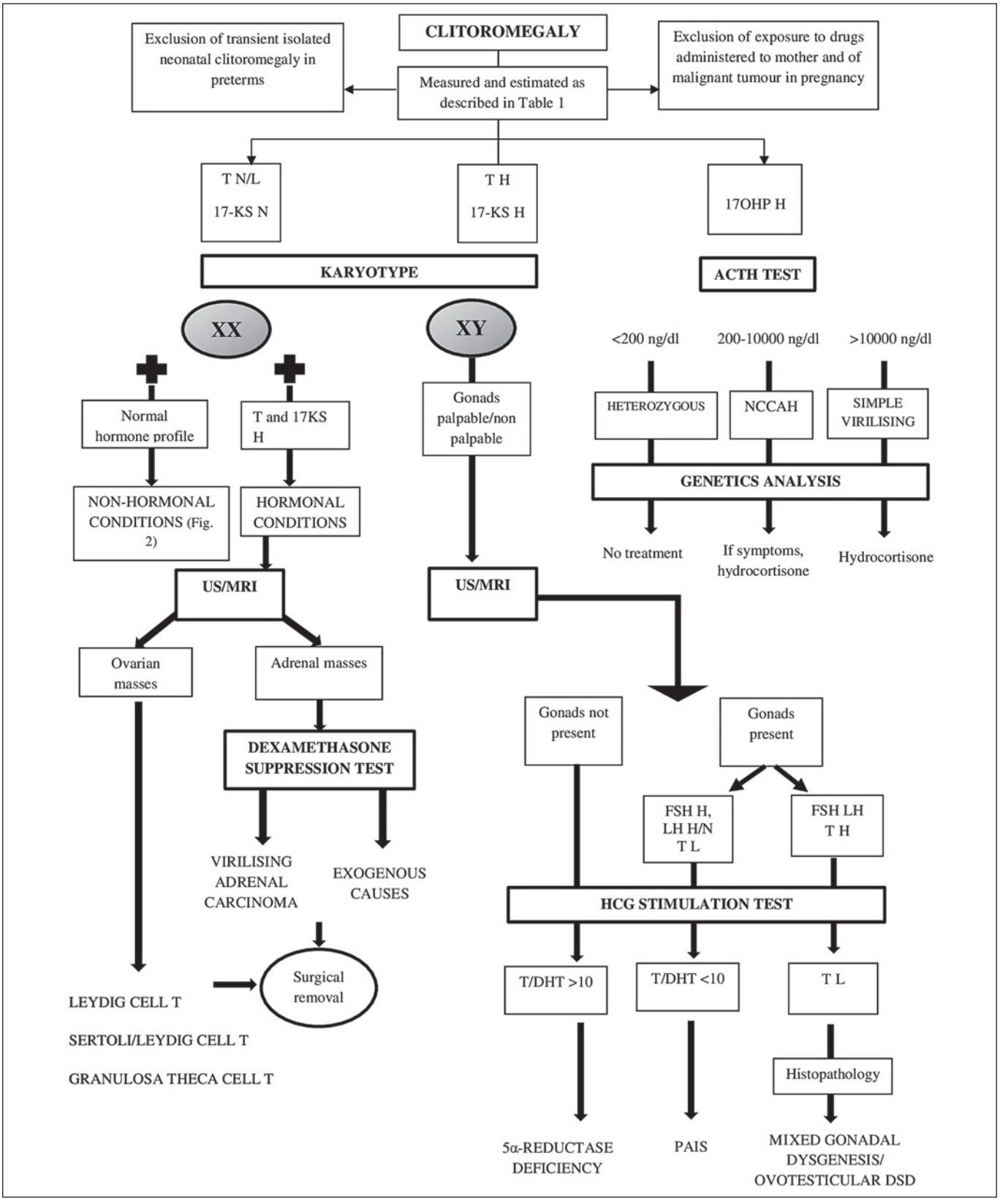

Fig. 2. Diagnostic procedure of clitoromegaly.

Table 3. Disorders of sex differentiation in 46,XX patients

Cause	Gene(s)	Syndrome	Genitalia
Genetic	*CYP21A2* *CYP11B1* *HSD3β2*	congenital adrenal hyperplasia	ambiguous genitalia
Androgen excess			
Fetal, fetoplacental, and maternal causes			
Masculizing tumors			
Polycystic ovary syndrome			

Table 4. Disorders of sex differentiation in 46,XY patients

Karyotype	Gene(s)	Syndrome	Genitalia
Disorders of hormone synthesis or action			
46,XY	*SRD5A2*	5α-reductase deficiency	clitoris-like phallus
46,XY	*AR*	partial androgen insensitivity syndrome	mild clitoromegaly
Sex chromosome disorders of sex development			
45,X/46,XY 45,X0/46,XY 45,X0/46,XY	*SRY*	mixed gonadal dysgenesis	variable, from clitoral enlargement to ambiguous genitalia
Ovotesticular disorders of sex development			
71% XX 20% XX/XY 7% XY	*SOX9, RSPO, NR5A1, DMRT1, SRY, MAP3K1*	true hermaphroditism	variable, from clitoral enlargement to ambiguous genitalia

lar DSD. The genital duct develops according to the ipsilateral gonad (Tables 3, 4).

Androgen Excess: Fetal, Fetoplacental, and Maternal Causes of 46,XX DSDs

Virilization of female infants due to exogenous factors may be attributed to virilizing tumors in the mother or to administration of hormonal medications (androgens, estrogens, or progestins) to the mother during pregnancy. Four cases due to estrogen administration (diethylstilbestrol) during pregnancy have been reported [Bongiovanni et al., 2016]. All patients had clitoral enlargement without hirsutism, the mothers had received no other hormone medications, and virilizing syndrome and any other cause of masculinization had been ruled out. Such paradoxical effect of estrogens on female genitalia is difficult to explain. It may conceivably be ascribed to a temporary adrenal hyperplasia caused by their action, as suggested by experimental embryology studies [Bongiovanni et al., 2016]. The virilizing effect of maternal androgens on the female fetus is easier to explain. Exposure to androgens between 8 and 14 weeks of pregnancy produces labioscrotal fusion and clitoral hypertrophy, whereas after 12 weeks it only induces clitoromegaly. Infants with clitoral hypertrophy and pigmentation of the labia have been described. After the diagnostic workup had excluded endogenous sources of androgens, examination of the mother demonstrated high testosterone levels, leading to a diagnosis of pregnancy luteoma, which is the most common cause of gestational hyperandrogenism, followed by ovarian tumor, placental aromatase deficiency, and iatrogenic causes [Parappil et al., 2009]. Seventy cases of fetal masculinization of female infants associated with oral progestin administered during gestation have been reported. Earlier studies have documented that oral and intramuscular progestins induced partial masculinization of the female fetus [Wilkins et al., 1958], as did long-term estroprogestin therapy during pregnancy [Voorhess, 1967]. The consequences of fetal exposure to danazol are well known. Danazol, an androgen (ethisterone) with anti-gonadotropic and androgenic properties, is prescribed for endometriosis and

benign breast disease, menorrhagia, and premenstrual syndrome. Its administration during gestation induced virilization of female fetuses characterized by clitoromegaly, fused labia, and urogenital sinus formation [Brunskill, 1992].

Other Causes of Virilization

Masculinizing Tumors

A variety of tumors secrete steroid hormones, including cancers derived from cells of the male and female reproductive tract, adrenal glands, central nervous system, and, less commonly, liver and pituitary gland. Their clinical manifestations are the result of androgen production. Clitoral enlargement has been described in a high percentage of prepubertal girls with adrenocortical carcinoma [Sandrini et al., 1997]. Virilization is more often associated with malignant tumors [Latronico et al., 2001] rather than with secreting adenoma. Rare cases of mild clitoromegaly have been reported in adolescent girls with androgen-secreting adrenocortical oncocytoma [Lim et al., 2010]. More often, clitoromegaly is associated with cancers derived from secreting tumors of the ovaries of which 20% are granulosa cell tumors. Juvenile granulosa cell tumor is an uncommon type derived from non-germ cell tissue that may present with clitoromegaly and signs of precocious puberty in girls [Schulin-Zeuthen et al., 2003]. Clitoromegaly has also been described in a premenarchal girl with a sex-cord stromal tumor [Park et al., 2011] and in a 12-year-old girl with malignant adrenal paraganglioma [Kitahara et al., 1993].

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by menstrual abnormalities and clinical or biochemical hyperandrogenism. It affects 9–18% of women of reproductive age. Typical symptoms, related to hyperandrogenism, may arise at any age and include premature or exaggerated adrenarche in childhood and hirsutism and menstrual abnormalities in adolescence and early adulthood. PCOS is also associated with infertility and glucose intolerance, which is a predisposing factor for diabetes mellitus and cardiovascular disease. Hyperandrogenism is described in 60–80% of patients with PCOS and is responsible for signs such as clitoral enlargement. However, the latter sign is reported to be infrequent [Azziz et al., 2009], probably because the external genitalia of these patients are rarely examined. A recent study of the external genitalia of women with and without PCOS has documented a significantly greater clitoral length in the PCOS group, whose presence alone was an accurate predictor of disease [Köşüş et al., 2016].

Syndromes Involving Virilization

Turner Syndrome

Turner syndrome is a female sex chromosome DSD that results from partial or complete loss of an X chromosome. Abnormalities include short stature and gonadal dysgenesis. Bergendi et al. [1997] described a case of clitoromegaly and Turner syndrome.

Antley-Bixler Syndrome

This condition is characterized by skeletal abnormalities that primarily affect the head and limbs, and little is known about its cause. Some patients have mutations in *FDFR2* (fibroblast growth factor receptor 2) [Tsai et al., 2001], whereas others have apparently altered steroidogenesis frequently associated with elevated 17-hydroxyprogesterone [Reardon et al., 2000]. The high levels of 17α-hydroxylase and 21α-hydroxylase reflect impaired steroid hydroxylation. This metabolome may last several years in patients with ambiguous genitalia, but obvious skeletal abnormalities are uncommon. Androgen metabolite excretion tends to be low in patients older than 2 months of age, but it may be elevated in newborns at the time of sex differentiation, causing androgen production. These levels may be too high for a female and too low for a male, producing masculinization and clitoromegaly in females and hypoplastic genitalia in males [Shackleton et al., 2004].

Syndromes without Virilization

Various syndromes related to nonhormonal conditions may cause clitoromegaly.

Fraser Syndrome

Fraser syndrome is a rare congenital disorder with a prevalence of 1/100,000 live births. Its pathogenesis is mainly related to the genes *FRAS1* and *FREM2*, which encode an extracellular matrix protein involved in the regulation of epidermal basement membrane adhesion and organogenesis during fetal life [Smyth and Scambler, 2005]. The syndrome chiefly involves cryptophthalmos, genital abnormalities of which the most common is clitoromegaly (36.8% of patients), and cutaneous syndactyly (31.6%). These findings, together with having a sibling affected by the disease, are the major diagnostic criteria for Fraser syndrome [Slavotinek and Tifft, 2002].

Donohue Syndrome

This syndrome is an autosomal recessive genetic disorder involving chromosome 19 in the coding sequence of the *INSR* gene (insulin receptor), which causes the production of inactive receptor molecules. Infants have massive hyperinsulinemia, often associated with glucose intolerance or frank diabetes mellitus with fasting hypoglycemia; associated clinical findings include acanthosis nigricans [Elders et al., 1982], ovarian hyperandrogenism in postpubertal females [Moller et al., 1996], hirsutism, oligomenorrhea, and infertility. These manifestations seem to be related to a specific effect of insulin on the skin and ovaries that is partly mediated by stimulation of insulin-like growth factor I receptor [Poretsky, 1991]. Besides a number of malformations, affected female infants commonly show hirsutism and clitoromegaly.

Seckel Syndrome

Seckel syndrome is an extremely rare inherited disorder characterized by growth delay prior to birth, resulting in a low birth weight. The growth delay continues after birth and leads to a short stature (dwarfism). The syndrome is associated with defective ATR-dependent DNA damage signaling [Griffith and Walker, 2007]. ATR is a serine/threonine-specific protein kinase involved in sensing DNA damage and in activating the DNA damage checkpoint that leads to cell cycle arrest [Sancar et al., 2004]. Clitoromegaly is one of the main manifestations of the syndrome [Ramalingam et al., 2012].

Apert Syndrome

Apert syndrome involves distinctive malformations such as craniosynostosis and severe syndactyly of the hands and feet. Its prevalence is 1/65,000 live births, and it is caused by a specific missense substitution in *FGFR2*, which maps to chromosome band 10q26, resulting in an increased amount of precursor cells that enter the osteogenic pathway. The abnormality ultimately leads to increased subperiosteal bone matrix formation [Gazi et al., 2014]. A keratinocyte growth factor receptor (KGFR)-mediated effect has also been uncovered by the observation that KGFR expression in fibroblasts is associated with the severity of syndactyly [Slaney et al., 1996]. Genitourinary anomalies are highly common, occurring in 10% of patients, and clitoromegaly ranks third in frequency [Cohen et al., 1993].

Proteus Syndrome

Proteus syndrome is a hamartomatous condition characterized by focal overgrowths that can involve any structure of the body [William et al., 2005]. Its incidence is less than 1/1,000,000 live births, and it is estimated that 120 individuals with the syndrome are currently alive worldwide [Biesecker, 2006]. Recently, a mosaic activating mutation in *AKT1* has been reported to be associated with the syndrome [Lindhurst et al., 2011]. Clitoral enlargement has been described in an 11-year-old together with asymmetry of both feet and a progressive asymmetric overgrowth of the lower limbs and toes [Criton et al., 1995].

Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is a constellation of congenital abnormalities and the most common overgrowth syndrome. It usually presents with macroglossia, abdominal wall defects, and gigantism. Its prevalence is 1/10,000 [Weksberg et al., 2005]. BWS is associated with abnormal gene transcription in 2 imprinted domains on chromosome 11p15.5, known as the BWS critical region. The region contains 2 domains: imprinting center 1 (IC1) regulates IGF2 and H19 expression in domain 1, and imprinting center 2 (IC2) regulates CDKN1C, KCNQ10T1, and KCNQ1 expression in domain 2 [Barlow, 1994]. A variety of nonrenal urological problems, including clitoromegaly, are described in these patients [Wong et al., 2011].

Klippel-Trenaunay Syndrome

Klippel-Trenaunay syndrome (KTS) is a rare congenital condition affecting both genders equally, where the blood and/or lymph vessels fail to form properly. Its cause is unknown. According to one theory, a mesodermal defect arising during fetal life induces the persistence of microscopic arteriovenous communications (AVCs) [Baskerville et al., 1985]. Other researchers hypothesize that intrauterine injury to the inferomedial lateral tract or to the sympathetic ganglia induces formation of microscopic AVCs [Bliznak and Staple, 1974]. Somatic abnormalities due to phakomatosis (disorder of neural crest tissue) and abnormal regulation of end capillaries by the sympathetic nervous system has been proposed as another possible cause [You et al., 1983]. A gene for KTS that disrupts vascular integrity by activating VE-cadherin and inhibits developmental and pathological angiogenesis through inactivation of AKT and PI3K has recently been identified [Zhang and Yao, 2016]. The 3 main features of KTS are naevus flammeus (port-wine stain), venous and lymphatic malformations, and soft tissue hypertrophy (including sometimes clitoromegaly) [Prabhavathy et al., 1994].

Russell-Silver Syndrome

Little more than 400 cases of Russell-Silver syndrome have been reported to date, with phenotypes varying from mild to classic and the incidence ranging from 1/3,000 to 1/100,000 newborns [Falkert et al., 2005]. Its characteristics are shared by several other genetic abnormalities, but the principal molecular mechanisms seem to be methylation abnormalities of chromosome 11p15 and maternal uniparental disomy for chromosome 7 (mUPD 7) [Gicquel et al., 2005]. The syndrome is a clinically and genetically heterogeneous congenital disorder, whose primary features are growth retardation, short stature, facial dysmorphism, and limb asymmetry. Clitoromegaly has also been described in these patients [Galli-Tsinopoulou et al., 2008].

Lipodystrophy

Congenital generalized lipodystrophy (CGL) is an autosomal recessive condition characterized by a significant lack of body fat and severe metabolic disruption [Garg, 2000]. Four types have been described. Type 1 is associated with mutations in 1-acylglycerol-3-phosphate O-acyltransferase 2 *(AGPAT2)*, a gene that is involved in the formation of phosphatidic acid which in turn is required for triacylglycerol and glycerophospholipid synthesis [Takeuchi and Reue, 2009]. Type 2, or Berardinelli-Seip syndrome, is associated with abnormalities in the multipass transmembrane protein seipin. The protein is localized to the endoplasmic reticulum and is essential for the structure of lipid droplets [Agarwal and Garg, 2006]. Type 3 CGL is caused by a mutation in the caveolin 1 gene, which encodes a fatty acid-binding protein on the plasma membrane (PM) of adipocytes that in response to the free fatty acid concentration translocates from the PM to lipid droplets [Garg and Agarwal, 2008]. Finally, type 4 involves mutations in the transcript release factor *(PTRF)* gene, which encodes a caveolar-associated protein required for the formation and localization of the caveolae and the correct function of polymerase I [Shastry et al., 2010]. Several studies have described clitoromegaly in CGL patients [Fontan and Couteau, 1956; Khandpur et al., 2011].

Nonhormonal Conditions

Neurofibromatosis

Neurofibromatosis is an autosomal dominant disorder with an incidence of approximately 1/3,000 live births. Characteristic findings are pigmented skin lesions (café-au-lait spots) and soft-tissue tumors arising from the neural sheath in all parts of the body. Involvement of the external genitalia is highly uncommon and mostly affects the clitoris and labia or extends to the urinary tract, especially the bladder. Participation of the clitoris alone has been reported infrequently, but in such cases the first sign is clitoromegaly. In a study of 236 families with type 1 neurofibromatosis, 4 patients had clitoral involvement, and in 3 of them the lesion was limited to the clitoris [Sutphen et al., 1995]. In childhood, several cases have been described secondary to a localized neurofibroma infiltrating the clitoral body, which in very rare cases involved the dorsal clitoral hood [Cost et al., 2009]. Sometimes clitoromegaly is the first sign of the disorder in very small girls [Karabouta et al., 2015]; at the time of presentation most patients do not meet the diagnostic criteria of neurofibromatosis. The first case of clitoris enlargement with neurofibromatosis type 2 or central neurofibromatosis was reported in 2003 [Yüksel et al., 2003]. Besides malignant schwannoma, histological examination usually identifies solitary or plexiform neurofibroma.

Epidermoid Cyst

Isolated clitoromegaly may be related to iatrogenic injury after genital mutilation. Female circumcision is still common in some rural areas. It is performed in various ways and often includes clitoridectomy [Rouzi et al., 2001; Bruni et al., 2009]. Inclusion cysts in the female external genitalia (clitoris, vulva, and even vagina) are a not uncommon complication following circumcision and are well documented in the literature. They are due to traumatic transplantation of the epidermis into intradermal or subcutaneous tissue with subsequent proliferation of epidermal cells [Schober et al., 2014]. Cysts have an outer wall of epidermis and a center filled with keratin material arranged into laminae. Epidermoid cysts are usually solitary, asymptomatic, slow-growing proliferations of epidermal cells, and clitoral epidermoid cysts need to be differentiated from other conditions involving the organ. An epidermoid cyst, whose clinical onset was related to accidental blunt trauma, has been described in a 9-year-old child; pathological examination disclosed an epidermoid cyst lined with stratified squamous epithelium without skin appendages and filled with keratinous material [Çelik et al., 2011]. Spontaneous, nontraumatic, epidermal inclusion cysts in the clitoris have also been described in pediatric female patients without a history of circumcision, and local excision resolved the patient's pain [Anderson-Mueller et al., 2009].

Other Tumors

Abnormalities of the clitoris may be associated with nonhormonal causes, such as benign or malignant tumor, although they are rare in childhood.

The most common lesions are hemangioma and neurofibroma, the latter generally related to neurofibromatosis. Cavernous hemangioma is a common neoplasm that can form anywhere in the body and appears as a lobulated mass. Only 5 cases of clitoromegaly secondary to hemangioma have been reported in young girls [Nayyar et al., 2014]. Misdiagnosis as adrenogenital syndrome may involve underestimation [Kaufman-Friedman, 1978].

The differential diagnosis of an irregular clitoral mass includes plexiform schwannoma, a benign slow-growing tumor of the nerve sheath. Despite the rich innervation found around the clitoris, only 3 cases of schwannoma and clitoral involvement have been reported. The diagnosis relied on histopathological examination of the lesion, because it is difficult to distinguish between schwannoma and neurofibroma [Llaneza et al., 2002; Azura et al., 2013]. Other isolated tumors include fibroma, leiomyoma, angiokeratoma, pseudolymphoma, and hemangiopericytoma [Maor-Sagie et al., 2010]. Notably, of 7 pediatric cases of angiomyxoma of the vulva mimicking clitoromegaly, 1 case involved the clitoral region. Spindle and stellate cells, identified in the myxoid matrix, lack metastatic potential but involve a high risk of local recurrence; however, no recurrence was detected in over 30 months. These tumors are found almost exclusively in the pelvis and the perineum of adult women, but when they arise in small girls they present as clitoral enlargement [Kawamura et al., 2017]. Malignant tumors, albeit extremely rare in girls, should be included in the differential diagnosis, because tumors like carcinoma, endodermal sinus tumor, sarcoma, and rhabdomyosarcoma may be a cause of clitoral hypertrophy [Gomes et al., 2013]. Finally, a mediastinal non-Hodgkin's lymphoma involving the clitoris has been described in a 2-year-old girl as the first sign of the disease with no other symptoms [Lim et al., 2010].

Nevus

Intradermal nevus presenting as clitoromegaly has been described in a 6-year-old child and is extremely rare [Mandal et al., 2009].

Pseudo-Clitoromegaly

Masturbation is normal in children and adolescents. In spite of its prevalence the pediatric literature is scanty. Masturbation is practiced at all ages and has been seen in utero. It is most common in children at about 4 years of age and again in adolescents. The primary site of genital stimulation is the penis in most males and the glans clitoris in most females [Kaplan, 1991]. Pseudo-hypertrophy of the clitoris due to masturbation has been described in small girls, where manipulation of the skin of the prepuce leads to repeated mechanical trauma with expansion of the labia minora, thus mimicking true clitoral enlargement [Wilkie et al., 1995].

Idiopathic Clitoromegaly

When the clitoromegaly occurs in the neonatal period, it is usually attributed to androgen stimulation secondary to CAH or to fetal androgen exposure. Transient isolated neonatal clitoromegaly has rarely been reported and was associated with increased androgen levels without unidentifiable causes, and the condition resolved spontaneously when the levels normalized. In one of these cases, a preterm baby girl received multiple blood transfusions from an adult man. Since after the withdrawal of blood transfusion, her testosterone levels and clitoris size normalized, and the clitoral enlargement was attributed to hyperandrogenism secondary to transfusion [Akçam and Topaloglu, 2003]. In other cases, clitoromegaly was detected in preterm female infants at birth or after the first few weeks of life [Dumont et al., 2009; Williams et al., 2013]. There was no other sign of virilization, and other pathological conditions were excluded by the finding of high levels of free testosterone. The serum steroid profile showed elevated 16-hydroxysteroid and 3β-hydroxy-5ene steroid metabolites. The karyotype was 46,XX in all patients. After an average period of 3 months, androgen levels declined, and clitoral size diminished without treatment. Despite an exhaustive workup, the cause of the hyperandrogenism remains unknown. According to one of the several hypotheses that have been advanced, the phenomenon is secondary to high levels of circulating androgens. In preterm girls the fetal zone of the adrenal cortex persists until the 40th gestational week and produces steroids, mainly dehydroepiandrosterone (DHEA) and its sulphate (DHEAS). Other hypotheses implicate an excess of luteinizing hormone or an elevated LH/FSH ratio [Greaves et al., 2008]. Alternatively, higher kisspeptin synthesis in the brain or placenta in extremely premature infants could contribute to elevate gonadotropin and androgen levels. If all hematochemical and hormonal parameters are normal and no other abnormality is noted, a diagnosis of idiopathic clitoromegaly is made. The condition is very unusual. Copcu and co-workers [2004] have reported 2 cases of acquired idiopathic clitoromegaly in-

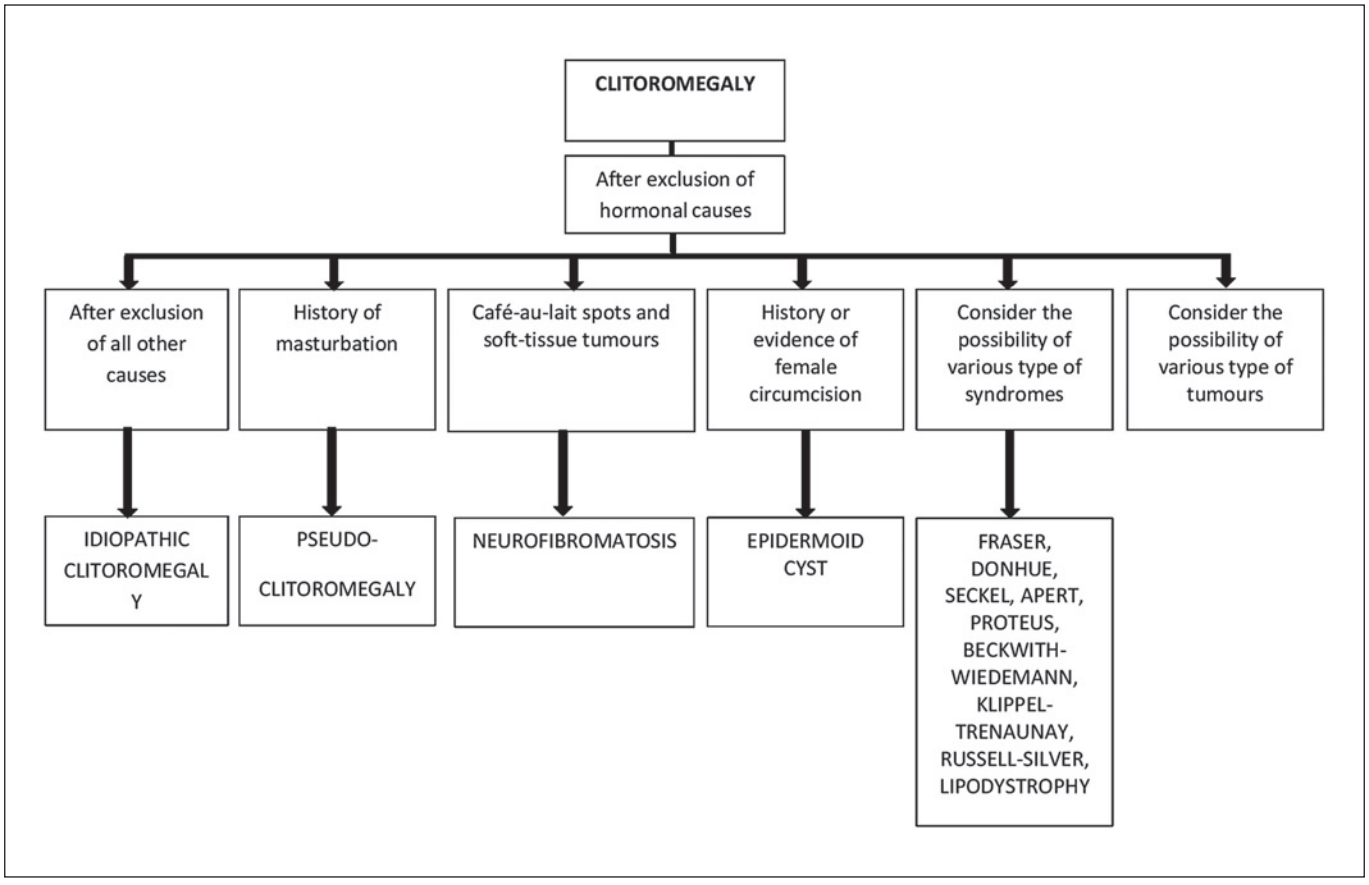

Fig. 3. Classification of clitoromegaly after exclusion of hormonal causes.

volving an adolescent and a child who had no history of exposure to medications, clitoral irritation secondary to masturbation, or gynecological or systemic abnormalities and had normal karyotype and hormonal tests. Recently, Kujur and co-workers [2016] have described a new case involving a 20-year-old woman with a negative history of clitoral irritation, hormone use or alteration, hirsutism, obesity, or systemic abnormality. Hayase and co-workers [2006] have reported a unique case of congenital prepubic sinus, previously diagnosed as idiopathic clitoromegaly, in a 12-year-old girl who had had clitoromegaly for some years. Congenital prepubic sinus is an extremely rare anomaly, especially in females. According to some authors, it originates from the skin overlying the pubic symphysis immediately superior to the base of the penis or clitoris and extending to but not communicating with the anterior wall of the bladder. In this patient the clitoral hypertrophy was due to chronic periclitoridean discharge. Albeit rare, this anomaly should be considered as a possible cause of clitoromegaly.

Diagnosis

The above considerations suggest that patients with clitoromegaly should undergo a comprehensive history, a thorough physical examination, a comprehensive endocrinological investigation, karyotyping, and genetic analysis. Histological examination may also be needed. However, it should be stressed that an irregular and asymmetric clitoris is usually related to a nonhormonal cause that should always be taken into account (Fig. 3).

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