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Chapter 2.1

Testicular microlithiasis in boys

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Abstract

In three boys aged 15, 9, and 10 years respectively scrotal ultrasound revealed testicular microlithiasis (TM). Two boys were free of symptoms and one suffered from testicular pain. TM is characterized by multiple echogenic foci within the seminiferous tubules with no acoustic shadowing. The pathophysiology is largely unknown. In adult men, TM prevalence has been reported to range from 0,2 to 29%. In boys the prevalence rate varies from 0,1 to 11,7%. There are indications that TM might be associated with malignant conditions of the testes. Although in adult men the method of follow-up is controversial, annual follow-up is usually recommended. In pediatric patients virtually no follow-up guidelines exist. Testicular self-examination, for example 3-monthly, and annual ultrasound in addition to physical examination might be warranted especially in boys with undescended testis who are already at risk for malignant transformation in the cryptorchid testis. Prognosis, as well as with regard to fertility, is largely unknown.

Introduction

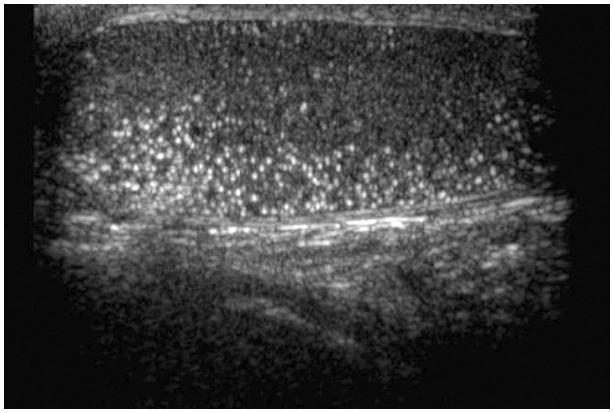
Testicular microlithiasis (TM) are small calcifications that can be found diffusely scattered or segmented in the testis parenchyma of one or both testis.[1] Calcifications in the testis, visible on x-ray, were first described in 1970 in a 4-year-old boy.[2] In adult males prevalence rates are described ranging from 0.9 to 29%; in boys these rates are less available. There are indications that, at least in men, TM is associated with fertility problems and testicular tumors. In adults, there is no consensus about the exact follow-up of the disease but annual follow-up is often recommended. For boys this is less clear. TM is usually found by co-incidence and it could be expected that with the increased use of ultrasound it will be more diagnosed in boys.[3]
The various aspects of this disorder are discussed referring to the case history of three boys with TM.

Cases

Case 1

A 15-year-old boy was referred for a painful right testis. At the age of 12 he was consulted by a clinical geneticist for impaired development, excessive height and arachnodactyly. Chromosomal examination revealed a normal male 46, XY karyogram and DNA research on the Fragile X syndrome was normal (repeat length of 19 in the FMR1 gene). There was also abnormality found by screening the urine for metabolic disorders. At ophthalmologic examination, there was no evidence for subluxation of the lens. His 12-year-old brother also suffered with impaired development, excessive height and arachnodactyly. Chromosome examination and investigations of the Fragile X syndrome were also normal in this boy.
An asthenic boy with arachnodactyly was seen at examination. His length was 194 cm (SDS between +2 and +2½) and his weight was 54 kg (SDS < -2). Examination of the genitalia externa showed no abnormalities: both testes were descended and the Tanner puberty state was P3G3. During examination of the testes innumerable microcalcifications were found in the right testis, mainly at the lateral side (see figure). In the left testis were also innumerable microcalcifications seen, diffusely scattered throughout the parenchyma. Ultrasound of the testes was also performed in his 12- and 13-year-old brothers on request of the parents which showed no abnormalities.

Figure 1
Transscrotal ultrasound of the right testis of the first patient (sagittal image). There are numerous, sharply definable microcalcifications seen which are testicular microlithiasis. The typical aspect of no acoustic shadowing could be seen.



Case 2

A 9-year-old boy was referred for an right undescended testis based on acquired undescended testis. He had no significant medical history. His length was 133.5 cm (SDS -1) and his weight was 26.5 kg (SDS -1) The right testis was positioned in the groin region. At the age of 11, at Tanner puberty stage P1G2, the right testis descended spontaneously. Scrotal ultrasound showed numerous small calcifications in both testes without acoustic shadowing, diffusely scattered throughout the parenchyma.

Case 3

A 10-year-old boy was referred for a left undescended testis based on acquired undescended testis. At the age of 4 months a perimembranic ventricular septal defect was surgically closed. As a result of feeding problems he was initially feeded via a nasogastric tube followed by a percutaneous gastro-enterostomy. From the age of 9 he was known with asthma and both respiratory and food allergies. Inhaled steroids (fluticasone initially after salmeterol / fluticasone) and, β-sympaticomimetics (salbutamol) were used. At the age of 8 a residual septal defect was surgically closed. At examination his length was 129 cm (SDS between -1 and -2) and his weight was 23 kg (SDS between -2 and -2 ½). The left testis was located in the groin region. At the age of 13, at Tanner puberty stage P2G3, orchidopexy was performed as a result of no spontaneous descent. Numerous calcifications were observed diffusely scattered throughout the parenchyma in both testis during ultrasound six months after surgery. On request of the parents ultrasound was also performed in his 8- and 16-year-old brother which showed no abnormalities.

Discussion

TM are small calcifications that can be found diffusely scattered or segmented in the testis parenchyma of one or both testis. On ultrasound it is characterized by 1 to 3 mm in diameter echogenic foci without acoustic shadowing. In grade 1, 5 -10 foci, in grade 2, 10 - 20 foci and in grade 3, > 20 foci are seen in one transducer field.[1] TM usually involves both testes with the calcifications equally distributed in the parenchyma. However, also segmental and clustered lesions can be seen.[4]

The cause of TM is not well known. It is histologically characterized by concrements of hydroxyapatite in the lumen of the seminiferous tubules[5] presumably caused by accumulation of celdebris of degenerated epithelial cells of the tubules in which glycoprotein attaches. Insufficient phagocytosis of the Sertoli cells might play a role in this process. Seminiferous tubules occlude due to this process resulting in atrophy of the tubules. This process could lead to impaired fertility. Some authors suggest that abnormalities in the basal membrane of seminiferous tubules play a primary role. There is also evidence that microlithiasis primarily originate in the interstitium outside the tubules and that the tubules are secondary compressed by the microliths.[6]

TM usually exists without clinical symptoms and the diagnosis is often made by co-incidence. Possible symptoms are testicular pain, as in the first patient, asymptomatic swelling or discomfort of the testis. Also hematospermia has been described.

In adult males prevalence rates ranging from 0.2 to 29% are described depending on kind of patients and methods used.[7,8] In asymptomatic men prevalence rates of 2.4 and 5.6% are found.[9] The prevalence of TM in boys is mainly unknown. The few studies performed show prevalence rates ranging from 0.1 to 11.7%.[10] The prevalence of TM in healthy boys is unknown.

Most of the boys who are diagnosed with TM are without symptoms, as the second patient. TM is also associated with a variety of disorders (see table). Most of these seem to be rather based on co-incidence than that they have a causal relation. In patients with pseudoxanthoma elasticum, a rare hereditary disorder of the soft tissue with calcification and fragmentation of elastic fibers, TM occurs in almost all patients.[11]

There are indications that TM is associated with testicular tumors.[4] In adults, up to 45% of the patients who are diagnosed with TM at presentation are also diagnosed with a testicular tumor. However, in adult men a testicular tumor is only occasionally found during follow-up.[12] In boys these prevalence rates vary from 0 to 12% but these data are only based on a few studies. Furthermore, there are also extra-testicular tumors reported in patients with TM without a primary testicular tumor. Also in TM a relatively high prevalence of carcinoma in situ (CIS), a premalignant condition, was found.[13]

Microcalcifications which are comparable to TM are also often found in testicular tumors.[14] The number of microliths seems to have no relation with the development of a testicular tumor.

The association of TM with undescended testes, as in the second and third patient,

Table 1
Overview of testicular microlithiasis and associated disorders.

Almost always

- pseudoxanthoma elasticum

Often

- testicular
  - malignant testis tumor
  - infertility/subfertility
  - undescended testis

Sporadic

- testicular
  - congenital
    - epididymic cyst
    - funiculus spermaticus cyst
    - hydrocele
    - varicocele
    - testicular dysgenesis
    - testicular atrophy
  - mechanical
    - after testicular torsion
    - after torsion of the testicular appendix
  - (para)neoplastic
    - benign testis tumor
  - post-infectious
    - (epididymo-)orchitis
- non-testicular
  - (para)neoplastic
    - extra-testicular tumor
    - leukemic infiltrate
    - non-Hodgkin lymphoma
    - after chemotherapy/radiation
  - syndrome/congenital
    - Klinefelter syndrome
    - Down syndrome
    - male pseudo-hermaphroditism
  - systemic disorders
    - AIDS
    - neurofibromatosis type 1
  - others
    - pulmonary alveolar microlithiasis
    - microcalcifications in central nervous system

has been described in several studies. Adult men with TM have often a history of cryptorchidism.[15] After orchidopexy for undescended testis prevalence rates are found of 9.5, 8.0 and 10.0%[16] and after testis biopsy, performed during orchidopexy, of 11.7%. One study reported that 10% of boys with TM and a (treated) undescended testis developed a testicular tumor.[17]

TM must be differentiated from other forms of intra-and extra-testicular calcifications.[18] Intra-testicular calcifications can be found in focal lesions after acute or chronic testis infarct, in granulomas (tuberculosis, sarcoidosis) after torsion or trauma of the testis, after (epididymo-) orchitis, after chemotherapy and / or radiation, in aberrant adrenal tissue and in benign and malignant testicular tumors and leukemic infiltrates.

Calcifications outside the testisparenchyma concern scrotoliths (known as “scrotal pearls”) which are isolated calcifications in the tunica vaginalis. Calcifications in the epididymis are often seen after an infection while calcifications in the appendix of the testis can occur after torsion.

The diagnosis TM can be made based on typical ultrasound images. Ultrasound criteria of TM are: five or more foci per transducer field without acoustic shadowing, scattered diffusely throughout the testisparenchyma and no loss of shape or volume of the testis. There is no indication for additional imaging of the chest and abdomen. Determination of serum tumor markers (lactate dehydrogenase, α-fetoprotein, β-human chorionic gonadotrophin) gives often no further information and is only indicated when a tumor is suspected on ultrasound. Chromosomal examination is not routinely performed. Ultrasound of the testes of siblings, as performed in the first and third patient, is not indicated.

The prognosis of TM in boys is unclear. The condition is not progressive and the number of calcifications seems not to increase in time. Spontaneous regression has occasionally been described in both adults and boys.[19] The fertility prognosis may be reduced as a result of the possible closure of the lumen of the seminiferous tubules by microliths[20] but this could not be confirmed by semen analysis.[21] This prognosis will also depend on whether there is a testicular tumor present at presentation or will develop in time.

There are no uniform guidelines regarding the follow-up of TM after diagnosis. Some authors suggest that follow-up is not necessary. Others recommendations vary from self-examination of the testes, biannual or annual ultrasound and physical examination[22], serial determination of serum tumor markers, imaging of the abdomen and thorax and even testisbiopsy to exclude CIS.

Since boys with TM and (treated) undescended testis appear to have an increased risk to develop a testicular tumor, it seems justifiable to perform any kind of follow-up in this group of patients. A 3-monthly self examination combined with annual ultrasound and physical examination could be considered.[23] For boys without any risk factors only 3-monthly self examination seems to be sufficient. Since testicular tumors are mostly present in the age group from 15 to 50 years, it seems justified to perform follow-up in boys only from the age of 15.

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