Urogenital abnormalities in male children with cystic fibrosis

H Blau, E Freud, H Mussaffi, M Werner, O Konen, V Rathaus

Background: Congenital bilateral absence of the vas deferens (CBAVD) is presumed to occur prenatally and is present in over 99% of adult males with cystic fibrosis (CF).

Aims: To describe ultrasonic features in male children with CF. We aimed to describe urogenital abnormalities, comparing pancreatic sufficient and insufficient CF patients.

Methods: Pelvic and scrotal ultrasonography were performed in 12 boys with CF aged 2–12 years and 16 age matched healthy controls.

Results: Nine patients had pancreatic insufficiency (PI); seven had two severe mutations and two had unknown mutations. Three boys were pancreatic sufficient (PS), two with splicing mutations (5T and 3849+10kb C–T respectively) and borderline sweat tests. Seminal vesicles were visualised in 5/12 patients and 8/16 controls, compared to non-visualisation reported in all adults with CBAVD. Testicular microlithiasis was found in 4/18 PI, 0/6 PS, and 0/32 control testes, compared to 0.6–1.4% in healthy males and 15% in CF adults; 7/18 PI, 4/6 PS, and 0/32 control testes were smaller than predicted for age. The epididymal head was non-homogeneous with cysts, hypo-, or hyper-echogenicity in 5/18 PI, 1/6 PS, and 0/32 control testes.

Conclusions: Genital abnormalities may occur early in CF, but are less common than described in adults. They are found more often in pancreatic insufficient than in pancreatic sufficient CF patients. However, a positive finding, if present, may aid in the diagnosis of the latter. A larger longitudinal study is recommended to better define the onset and progression of urogenital abnormalities.

Cystic fibrosis (CF) is caused by mutations of the CFTR gene, which cause abnormal chloride concentration across the apical membrane of epithelial cells in the airways, pancreas, intestine, sweat glands, and the male genital system. Congenital absence of the vas deferens (CBAVD) is present in 99% of adult males with CF. However, penetrance of this phenotype is variable in adult males with CF and pancreatic sufficiency. While the ultrasonic appearance of the adult male reproductive tract in cystic fibrosis (CF) has been well described, there is little information regarding sonography of the urogenital tract in male children with CF. Interestingly, in fetuses aborted at 12–18 weeks with two severe CF mutations, the vas deferens was histologically normal, suggesting that CBAVD in CF may develop with time, because of inspissation of secretions and secondary atresia, rather than agenesis. It remains unclear at what stage this occurs.

We performed a small cross sectional study of male prepubertal children with CF, to determine the presence and severity of abnormalities as visualised by sonographic examination of the urogenital tract. Findings were compared for pancreatic sufficient and insufficient subjects.

METHODS

Patient selection

Twelve boys with cystic fibrosis up to age 12 years were selected at random from the Kathy and Lee Graub Cystic Fibrosis Center, Schneider Children’s Medical Center of Israel. As a control group, 16 healthy boys of similar ages underwent sonographic examination by the same paediatric radiologists. In all cases, parents gave informed consent. Findings were compared to published normal paediatric values.

Sonographic examination

Sonographic examination was performed by an experienced radiologist at the Pediatric Radiology Unit, Sapir Medical Center. Imaging of the urinary tract and scrotum was performed using an HDI 5000 SonoCT (ATL) system. A convex 2–5 or 5–8 MHz transducer was used for the abdominal imaging, depending on the age and body habitus of the children. A 5–12 MHz linear transducer was used for the scrotal examination.

The testes were examined after elevation and immobilisation by gently placing a rolled up towel posterior to the scrotum in a vertical position between the legs.

Morphology of kidneys, ureters, bladder, seminal vesicles, inguinal canal, testes, and epididymis were recorded and compared to normal findings in children. Dimensions of testes were measured and compared to predicted values for length and volume. Volume was calculated using the simplified formula of \( V = \frac{4}{3} \pi r^3 \). We elected not to perform rectal ultrasound because of the more invasive nature of this test.

Clinical assessment

The following data were recorded for the 12 boys selected: age, height, and weight percentile at the time of examination; sweat chloride concentrations; pulmonary function tests performed using a Medgraphics spirometer in all boys able to cooperate; and Shwachman score calculated from the clinical state and chest x ray findings. The patients were divided into two groups: pancreatic insufficient (PI) and pancreatic sufficient (PS) according to their pancreatic function. For this purpose, pancreatic insufficiency was defined as a coefficient of fat absorption (as calculated from recorded dietary fat intake and a three day faecal fat collection) of <93% and/or a

Abbreviations: CBAVD, congenital bilateral absence of the vas deferens; CF, cystic fibrosis; PI, pancreatic insufficiency; PS, pancreatic sufficiency.
facial elastase of ≤200 µg/g stool. Boys with levels above these were termed pancreatic sufficient (PS).

**Mutation analysis**

All patients were screened for the CFTR mutations previously identified in the Israeli CF population.

**RESULTS**

**Clinical phenotype and correlation with CFTR mutations**

 Patients with pancreatic insufficiency

Nine boys were shown to be pancreatic insufficient (PI) (table 1). Seven of these were homozygous or compound heterozygotes for the genotypes ΔF508, W1282X, G542X, S549R, and 405+1G→A. These mutations have previously been associated with severe disease including pancreatic insufficiency, early age at diagnosis, and higher sweat chloride concentrations. Two brothers of Arab Moslem origin had a similar classic CF phenotype but no identified mutations. PI patients all had evidence of CF related lung disease as well as pancreatic insufficiency. However, as is now frequently the case in young patients, they had evidence of CF related lung disease as well as pancreatic insufficiency, early age at diagnosis, and higher sweat chloride concentrations. Two brothers of Arab Moslem origin had a similar classic CF phenotype but no identified mutations. PI patients all had evidence of CF related lung disease as well as pancreatic insufficiency. However, as is now frequently the case in young boys with CF, the male genital tract was shown to be normal in all patients. Infertility in adult CF males was first described in 1968. Urogenital pathology includes absence or atrophy of the vas deferens, tail and body of the epididymis, and seminal vesicles. Congenital absence of the vas deferens (CBAVD) with azoospermia appears to be the most constant feature in CF, even when clinical scores are excellent. Furthermore, even in adult males with a mild CF phenotype, obstructive azoospermia has been suggested as a major diagnostic criterion. This small cross sectional study is the first to describe ultrasound findings in male CF patients. As the clinical distinction between the spermatic cord and vas is more difficult in infants and children than in adults, genital ultrasound is essential for any definition of reproductive tract pathology, short of direct exploration. We therefore examined the urogenital tract in boys with CF. Little is known of the onset or natural progression of CF genital pathology in children. In a study of 12 and 18 week aborted fetuses with CF, the male genital tract was shown to develop normally at first. The vas deferens appeared similar to

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age (y)</th>
<th>Sweat chloride</th>
<th>CFTR mutations</th>
<th>FEV1</th>
<th>Wt</th>
<th>Ht</th>
<th>Sh. score</th>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>69</td>
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<td>–</td>
<td>3</td>
<td>3</td>
<td>77</td>
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<td>2</td>
<td>3</td>
<td>100</td>
<td>W1282X/W1282X</td>
<td>98%</td>
<td>50</td>
<td>75</td>
<td>92</td>
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<tr>
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<td>5</td>
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<td>94%</td>
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<td>10</td>
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<td>25</td>
<td>85</td>
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<tr>
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<td>7</td>
<td>76</td>
<td>W1282X/G542X</td>
<td>105%</td>
<td>95</td>
<td>40</td>
<td>90</td>
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<td>8</td>
<td>99</td>
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<td>50</td>
<td>98</td>
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<tr>
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<td>9</td>
<td>90</td>
<td>S549R/S549R</td>
<td>77%</td>
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<td>10</td>
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<td>8</td>
<td>10</td>
<td>84</td>
<td>W1282X/ΔF508</td>
<td>102%</td>
<td>25</td>
<td>20</td>
<td>89</td>
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<tr>
<td>9</td>
<td>10</td>
<td>97</td>
<td>W1282X/ΔF508</td>
<td>87%</td>
<td>50</td>
<td>50</td>
<td>98</td>
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</table>

FEV₁, forced expiratory volume in 1 second; Wt, weight, percentile for age; Ht, height, percentile for age; Sh. score, Shwachman score.

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<th>Pt no.</th>
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<th>Sweat chloride</th>
<th>CFTR mutations</th>
<th>FEV1</th>
<th>Wt</th>
<th>Ht</th>
<th>Sh. score</th>
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<td>10</td>
<td>5</td>
<td>45</td>
<td>ΔF508/3849+10kb C→T</td>
<td>106%</td>
<td>50</td>
<td>28</td>
<td>95</td>
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<td>107</td>
<td>ΔF508/unknown</td>
<td>85%</td>
<td>10</td>
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<td>84</td>
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<tr>
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<td>12</td>
<td>44</td>
<td>W1282X/5T</td>
<td>115%</td>
<td>75</td>
<td>65</td>
<td>100</td>
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</table>

FEV₁, forced expiratory volume in 1 second; Wt, weight, percentile for age; Ht, height, percentile for age; Sh. score, Shwachman score.

Abnormalities of epididymis and testes were seen, even in the bladder. Abnormalities within the epididymis and testicular micro lithiasis were found in 4/18 testes of PI boys, and in one case was present bilaterally. There were no cases of micro lithiasis in six testes of PS boys or 32 testes of healthy controls. In the CF patients, testes were often smaller than predicted for age: 7/18 in PI patients and 4/6 in PS patients. All 32 testes in healthy controls were within predicted normal values for age. Abnormalities within the epididymis and testicular microlithiasis were found in the same patient. Seminal vesicle visualisation was less consistent, in both CF patients and controls, and non-visualisation could occasionally have been related to technical factors such as incomplete filling of the bladder.

**DISCUSSION**

Infertility in adult CF males was first described in 1968. Urogenital pathology includes absence or atrophy of the vas deferens, tail and body of the epididymis, and seminal vesicles. Congenital absence of the vas deferens (CBAVD) with azoospermia appears to be the most constant feature in CF, even when clinical scores are excellent. Furthermore, even in adult males with a mild CF phenotype, obstructive azoospermia has been suggested as a major diagnostic criterion. This small cross sectional study is the first to describe ultrasonic features in male CF children. As the clinical distinction between the spermatic cord and vas is more difficult in infants and children than in adults, genital ultrasound is essential for any definition of reproductive tract pathology, short of direct exploration. We therefore examined the urogenital tract in boys with CF. Little is known of the onset or natural progression of CF genital pathology in children. In a study of 12 and 18 week aborted fetuses with CF, the male genital tract was shown to develop normally at first. The vas deferens appeared similar to
Epithelial cells of the epididymal head where most secretion occurs. There is little expression in the testis or downstream in the long, tortuous ducts and seminal vesicles. Presumably, epididymal CFTR dysfunction results in abnormal glycoprotein secretions and distal obstruction, with progressive duct atrophy and infertility in male adults with CF.

Secondary changes were also found proximally, within the testes. The high incidence of testicular microlithiasis in boys with CF and pancreatic insufficiency in this study is consistent with that described in adults with CF and CBAVD. Microlithiasis in healthy children is exceedingly rare, and in adult males is about 1%. The absence of microlithiasis in our PS subjects again suggests milder disease in this group. Both PI and PS patients had somewhat smaller testes, as has been described pathologically and by ultrason in adults.

Although numbers in this study are small, genital abnormalities appeared less frequent in patients with PS than PI. CF with normal pancreatic function is associated with variable CFTR expression, sweat chloride, and lung and genital disease. Patients are more susceptible to environmental influence as well as modifier genes, and males may be fertile despite severe lung disease. At the other end of the spectrum, CBAVD may be a solitary finding as a result of exquisite sensitivity of the genital tract to CFTR dysfunction. If genital ultrasound does identify abnormalities, these would be extremely helpful in the diagnosis of challenges cases of atypical CF in children. Patients may have strongly suggestive pulmonary disease but normal pancreatic function, unidentified genetic mutations, and normal or borderline sweat tests. Nasal potential difference is technically difficult to measure in young children and may be inconclusive. We propose that sonographic urogenital abnormalities be made a criterion for CF diagnosis in boys with mild CF, as is recommended for CBAVD in adults with atypical CF.

In an era of developing therapies directed at CFTR dysfunction, it is important to sonographically follow boys with classic CF, atypical CF, and even asymptomatic brothers of men with CF or CBAVD who have CFTR mutations. By means of this diagnostic modality and a larger cohort of patients, the onset and progression of urogenital abnormalities may be better defined. Hopefully, in the near future, these may be prevented by timely CFTR related therapy.

### Table 3  Ultrasound findings in pancreatic insufficient boys

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age (y)</th>
<th>Seminal vesicles</th>
<th>Testicular length (cm)/ volume (ml)</th>
<th>Testicular microlithiasis</th>
<th>Epididymis</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>NV</td>
<td>1.4/0.4 (+)</td>
<td>1.2/0.4 (+)</td>
<td>−</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>NV</td>
<td>1.8/0.9 (+nl)</td>
<td>1.7/0.7 (nl)</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>NV</td>
<td>1.6/0.5 (&lt;)</td>
<td>1.2/0.4 (&lt;)</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>V</td>
<td>1.6/0.7 (+)</td>
<td>1.4/0.7 (+)</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>V</td>
<td>1.8/0.9 (+nl)</td>
<td>1.7/0.8 (nl)</td>
<td>−</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>V</td>
<td>1.9/0.9 (+nl)</td>
<td>1.8/0.8 (nl)</td>
<td>−</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>V</td>
<td>1.6/0.8 (+nl)</td>
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<tr>
<td>8</td>
<td>10</td>
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<td>1.5/0.7 (+nl)</td>
<td>−</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>V</td>
<td>2.0/1.4 (+nl)</td>
<td>1.9/1.2 (&lt;)</td>
<td>−</td>
</tr>
</tbody>
</table>

R, right; L, left; nl, normal; <, smaller than normal for age; ech, hyperechogenic; nhom, non-homogenous; V, visualised; NV, non-visualised.

### Table 4  Ultrasound findings in pancreatic sufficient boys

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age (y)</th>
<th>Seminal vesicles</th>
<th>Testicular length (cm)/ volume (ml)</th>
<th>Testicular microlithiasis</th>
<th>Epididymis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>V</td>
<td>1.5/0.5 (+nl)</td>
<td>1.4/0.4 (+nl)</td>
<td>−</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>NV</td>
<td>1.2/0.5 (&lt;)</td>
<td>1.3/0.7 (+)</td>
<td>−</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>V</td>
<td>2.4/4.6 (+nl)</td>
<td>2.7/8.0 (nl)</td>
<td>−</td>
</tr>
</tbody>
</table>

R, right; L, left; nl, normal; <, smaller than normal for age; V, visualised; NV, non-visualised.
ACKNOWLEDGEMENT
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REFERENCES
1 Doull J. Recent advances in cystic fibrosis. Arch Dis Child 2001; 85:65–6

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Surgery for both hips in severe cerebral palsy
Up to 60% of children with quadriplegic cerebral palsy have unstable hips. Bilateral subluxation or dislocation of the hip may ensue and is often accompanied by pelvic obliquity and spinal deformity. The “windswept” deformity frequently develops with posterior subluxation of the adducted hip and anterior displacement of the opposite, abducted, hip. Hip pain may become intractable and care difficult. An orthopaedic team in Bristol (KL Owens and colleagues. Journal of Bone and Joint Surgery 2001; 83:1161–7) has assessed the results of bilateral hip surgery. They reviewed the notes of 30 children (60 operated hips, 18 girls, mean age 7.7 years) who had simultaneous bilateral combined soft tissue and bone surgery between 1991 and 1997. In 19 children the cerebral palsy was classified as dystonic and in 11 hypertonic. All had windswept deformity, 20 to the right and 10 to the left. The indications for surgery were increased asymmetry, radiological subluxation or dislocation, or pain. All patients had bilateral femoral varus derotation osteotomies and selected patients had bilateral or unilateral (adducted hip) acetabuloplasty. All hips were fully reduced at the end of operation. Most patients had release procedures involving poas, adductor, gluteus maximus, or tensor fascia lata muscles. A full hip spica was applied for 6 weeks after operation and each patient went home with a spica transporter. Follow up assessments were made at an average of 3 years. The mean range of combined abduction and adduction in flexion increased from 97° to 135° and fixed flexion decreased from 15° to 8°. In most patients, however, the windswept deformity did not change significantly. Of 50 hips with complete pre- and postoperative x rays 36 were subluxed or dislocated before operation and eight were subluxed afterwards. The overall level of mobility improved in a few patients. Thirteen patients had hip pain before operation but only two of these continued to have pain after operation. Three patients had supracondylar fractures of the femur postoperatively, one had trochanteric bursitis, one a sinus over a plate, and one a plaster sore. Twenty-three of 25 carers said the child was easier to handle and 22 expressed overall satisfaction with the management of their child.
Bilateral bone and soft tissue surgery may relieve pain and make care easier for children with severe quadriplegia, windswept deformity, and displaced hips.

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Blau, Freud, Mussaffi, et al

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