Deficiency of 17,20-lyase causing giant ovarian cysts in a girl and a female phenotype in her 46,XY sister: Case report

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A 13-year-old girl was referred because of progressive abdominal pain caused by ovarian torsion and giant ovarian cysts. Secondary sexual characteristics were absent. Hormone analysis revealed markedly elevated serum levels of progesterone and 17-hydroxyprogesterone in combination with very low peripheral concentrations of C19 steroids (dehydroepiandrosterone and androstenedione) and estrogens. Serum concentrations of FSH and LH exceeded the upper limit of normal levels in adult women. The patient’s 16-year-old 46,XY sibling showed a female phenotype with similar hormonal disturbances. Both siblings were found to be compound heterozygotes for two mutations in the CYP17 gene: an R347C mutation in one allele and a 25-base pair deletion in exon 1 in the other. The resulting block in 17,20-lyase activity caused an inability to synthesize androgens and estrogens, and increased levels of gonadotrophins due to a lack of negative feedback. The increased levels of gonadotrophins most likely stimulated growth of the ovarian cysts. The administration of a GnRH antagonist reduced the size of the cysts within a few weeks. At present, the girl is being treated with a combination of a GnRH agonist and hormone replacement therapy.

Key words: gene mutation/17,20-lyase deficiency/ovarian cysts/P450c17

Introduction
The cytochromes P450 form a family of enzymes which catalyse many oxidative processes. Some distinct P450 enzymes play key roles in steroidogenesis (Speroff et al., 1999; see Figure 1). One of the latter enzymes, P450c17, which is encoded by CYP 17, contains both 17β-hydroxylase and 17,20-lyase activities (Miller et al., 1997; Geller et al., 1999; Biason-Lauber et al., 2000). To date, 20 different missense mutations in the CYP 17 gene have been identified, leading to inactivation of the hydroxylase and/or lyase activities (Van den Akker et al., 2002). The degree of inactivation is dependent on the type and localization of the mutation in the gene.

In most situations the combined deficiency occurs, but several cases of isolated 17,20-lyase deficiency have also been described (Zachmann et al., 1972; Goebelsmann et al., 1976; Van den Akker et al., 2002). Affected 46,XY individuals are male pseudohermaphrodites with ambiguous or female external genitalia as a result of impairment of testosterone synthesis in the testes (Zachmann et al., 1982; Oei et al., 1995; Katsumata et al., 2001). One group (Larrea et al., 1983) published a case report about an XX female individual with hypergonadotrophic hypogonadism due to 17,20-lyase deficiency. These authors described clinical features of primary amenorrhoea and sexual infantilism in combination with elevated serum levels of progesterone and 17-hydroxyprogesterone (17-OHP) and anestrogenism. The present report describes a 46,XX child with a female phenotype and enlarged ovarian cysts with elevated gonadotrophins. She had an older 46,XY sibling with a female phenotype who has been described previously (patient 3 in Van den Akker et al., 2002). In the present report, mutations of the CYP17 gene were ascertained in the 46,XX girl and her mother, and the effects of treatment of the girl with GnRH analogues described.

Case report
A 13-year-old girl in whom menarche and puberty had not yet occurred was referred by her paediatrician for gynaecological investigation because of progressive abdominal pain. Abdominal pelvic ultrasound and magnetic resonance imaging revealed the presence of a cervix, a uterus and multiple ovarian cysts. On physical examination, the patient was found to be a healthy child with a normal 46,XX karyotype and blood pressure 140/80 mmHg. The hymen was normal, so an imperforated hymen and haematocolpus could be excluded. Signs of sexual maturation were absent, as was masculinization. Carpus X-radiographs were consistent with a bone age of 11.5 years. Hormone analysis revealed markedly elevated
serum 17-OHP and progesterone levels, in combination with very low levels of androstenedione, dehydroepiandrosterone (DHEA) and sex steroids estradiol (E2) and testosterone (Table I). LH and FSH levels were elevated for a premenarchal girl, and also exceeded the upper end of the normal level in an 17-month-old girl, and also exceeded the upper end of the normal level in an 10-year-old girl. Initially, it was thought that the girl had a nulliparous phenotype, and she was raised as a girl. At the age of 10 years, after analysis of the androgen receptor gene, the girl was returned. Further exploration revealed this child to have a 17,20-lyase deficiency (Van den Akker et al., 1983). Histological examination of the cyst fluid revealed the presence of granulosa cells. Some oocytes were found in biopsy samples taken from the ovaries, predominantly in the primordial follicles. Following the laparoscopic procedure, the girl experienced temporal relief from her complaints, and hormone replacement therapy was started with a combined contraceptive pill containing 30 μg ethinylestradiol and 150 μg levonorgestrel. However, within a few weeks she suffered again from episodic abdominal pain, and enlarged ovarian cysts were observed on sonography. She was treated with a GnRH antagonist (cetrorelix 0.25 mg s.c., daily) in order to obtain a rapid reduction in cyst size, and this was followed by relief of the complaints. Thereafter, in order to suppress LH and FSH levels permanently and to initiate sexual development, the girl was started on GnRH-agonist and hormone replacement therapy, with triptorelin and E2 (0.1 mg s.c. and 5 μg/kg bodyweight daily respectively). Later, 10.8 mg goserelin s.c. every 3 months was prescribed, instead of the daily triptorelin. During the last year, the patient was found to have normally sized ovaries without cysts, while LH and FSH were each down-regulated and the serum progesterone and 17-OHP levels were reduced, though not normalized (Table I). Withdrawal bleedings have not yet occurred. At present—at about 18 months after her initial complaints—the girl receives 20 μg E2/kg bodyweight daily, has developed some secondary signs of puberty, and is still growing.

The increasing abdominal pain necessitated a diagnostic laparoscopy, whereupon a large number of giant ovarian cysts (diameter ranging from 2–6 cm) with ascites imitating ovarian hyperstimulation syndrome were observed. The enlarged ovaries each measured about 12×15 cm. Most of the cysts were emptied by puncture, and the double-twisted right ovary was returned. Further exploration revealed a normally sized infantile uterus and normal tubes. Samples of fluid taken from four cysts contained high levels of progesterone and 17-OHP (Table III). The levels of androstenedione, testosterone and E2 in these fluid samples were below the normal ranges described by others (diZerega et al., 1983). Histological examination of the cyst fluid revealed the presence of granulosa cells. Some oocytes were found in biopsy samples taken from the ovaries, predominantly in the primordial follicles. Following the laparoscopic procedure, the girl experienced temporal relief from her complaints, and hormone replacement therapy was started with a combined contraceptive pill containing 30 μg ethinylestradiol and 150 μg levonorgestrel. However, within a few weeks she suffered again from episodic abdominal pain, and enlarged ovarian cysts were observed on sonography. She was treated with a GnRH antagonist (cetrorelix 0.25 mg s.c., daily) in order to obtain a rapid reduction in cyst size, and this was followed by relief of the complaints. Thereafter, in order to suppress LH and FSH levels permanently and to initiate sexual development, the girl was started on GnRH-agonist and hormone replacement therapy, with triptorelin and E2 (0.1 mg s.c. and 5 μg/kg bodyweight daily respectively). Later, 10.8 mg goserelin s.c. every 3 months was prescribed, instead of the daily triptorelin. During the last year, the patient was found to have normally sized ovaries without cysts, while LH and FSH were each down-regulated and the serum progesterone and 17-OHP levels were reduced, though not normalized (Table I). Withdrawal bleedings have not yet occurred. At present—at about 18 months after her initial complaints—the girl receives 20 μg E2/kg bodyweight daily, has developed some secondary signs of puberty, and is still growing.

The index patient’s 16-year-old genetically male ‘sister’ had the same hormonal disturbances. At the age of 2 months, this new-born with a female phenotype had bilateral inguinal hernias which contained testes. Prophylactic gonadectomy was performed a few months later. The karyotype was shown to be 46,XY, and she was raised as a girl. At the age of 2 months, this new-born with a female phenotype had bilateral inguinal hernias which contained testes. Prophylactic gonadectomy was performed a few months later. The karyotype was shown to be 46,XY, and she was raised as a girl. Initially, it was thought that she suffered from androgen insensitivity syndrome, but at the age of 10 years, after analysis of the androgen receptor gene, re-evaluation revealed this child to have a 17,20-lyase deficiency (Van den Akker et al., 2002). Her blood pressure was 140/80 mmHg. For reason of comparison, hormone levels measured in this patient at the age of 10 years after gonadectomy are included in Table I. The medical history of this case only became known to the gynaecologist following laparoscopy of the index patient.
have been male pseudohermaphrodites with ambiguous or female external genitalia (Zachmann et al., 1982; Oei et al., 1995). One group (Biglieri et al., 1966) were the first to describe 17α-hydroxylase deficiency in a female individual with primary amenorrhea, and a case study was subsequently reported (Mallin, 1969) concerning two sisters with amenorrhea, hypokalaemia, hypertension and cystic ovaries, based on 17α-hydroxylase deficiency. An absence of the enzyme led to a deficient sex steroid synthesis on the one hand and a reduced cortisol synthesis on the other hand. Another group (Pertzeran et al., 1981) described a 15-year-old girl with an absence of sexual development, polycystic ovaries and hypertension due to 17α-hydroxylase deficiency. Finally, a report was made about a female individual with hypergonadotrophic hypogonadism due to 17,20-lyase deficiency. Initially, the girl was treated with an oral contraceptive to suppress gonadotrophins, but within a few weeks after the laparoscopy she had suffered again from episodic abdominal pain caused by enlarged ovarian cysts, probably because the estrogen dose was inadequate to suppress the gonadotrophin levels. As a higher estrogen dose might have created a risk to the girl's final body height, she was further treated with a GnRH antagonist in order to suppress the cysts rapidly. Later, treatment was switched to a GnRH agonist in combination with estrogens in order to initiate sexual development. After suppression of the gonadotrophins with the GnRH-agonist, concentrations of progesterone and 17-OHP. Initially, the girl was treated with an oral contraceptive to suppress gonadotrophins, but within a few weeks after the laparoscopy she had suffered again from episodic abdominal pain caused by enlarged ovarian cysts, probably because the estrogen dose was inadequate to suppress the gonadotrophin levels. As a higher estrogen dose might have created a risk to the girl’s final body height, she was further treated with a GnRH antagonist in order to suppress the cysts rapidly. Later, treatment was switched to a GnRH agonist in combination with estrogens in order to initiate sexual development. After suppression of the gonadotrophins with the GnRH-agonist, concentrations of progesterone and 17-OHP were each reduced to levels comparable with those in the gonadectomized sister. If the girl had not developed enlarged ovaries, she would most likely have been referred some years later with primary amenorrhea and an absence of any signs of puberty.

In the present patient, the synthesis of cortisol was not (or was only slightly) impaired under basal circumstances, because of residual 17α-hydroxylase activity. An ACTH stimulation test showed a low to normal basal level of cortisol, which did not respond to ACTH (Table II), and this was suggestive of a partial 17α-hydroxylase deficiency. It is questionable whether this could be regarded as a mild form of glucocorticoid insufficiency, as the adrenal glands should be able to produce corticosterone, which also has glucocorticoid activity.

Questions remain about the girl’s chances of future pregnancy, however. Based on the results of a previous study (Schoot et al., 1994), it was apparent that ovarian stimulation with recombinant FSH in hypogonadotrophic women resulted in ovarian follicle development to the pre-ovulatory stage, with no or only a minor increase in estradiol concentrations. Others (Rabinovici et al., 1989; Pellicer et al., 1991) described successful IVF after oocyte retrieval from women with combined 17α-hydroxylase/17,20-lyase and 17,20-lyase deficiency respectively. Hence, it cannot be taken for granted that a

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Unit</th>
<th>Reference value follicular fluid</th>
<th>Case 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>nmol/l</td>
<td>31 300 ± 10 500</td>
<td>439–12 700</td>
</tr>
<tr>
<td>17-OH progesterone</td>
<td>nmol/l</td>
<td>4800 ± 600</td>
<td>700–16 600</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>nmol/l</td>
<td>275 ± 80</td>
<td>7.9–8.0</td>
</tr>
<tr>
<td>Testosterone</td>
<td>nmol/l</td>
<td>25 ± 7</td>
<td>&lt;0.3–13.3</td>
</tr>
<tr>
<td>Estradiol</td>
<td>nmol/l</td>
<td>9505 ± 44 81</td>
<td>0.6–35.8</td>
</tr>
</tbody>
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aData (mean ± SEM) in control follicular fluid (from diZerega et al., 1983)

bRange of concentrations found in samples from three to four different cysts.
lack of endogenous estrogen production automatically leads to a failure of follicular maturation. An important point here is how to deal with the ethical dilemmas related to the inheritance of a disease in case of reproduction.

In conclusion, the present case report illustrates the clinical expression of an identical rare genetic disorder in a female and a male proband. Both were compound heterozygotes for the same mutations in the CYP17 gene, resulting in a 17,20-lyase deficiency, and as a consequence the circulating levels of sex steroids were either absent or extremely low. Although for both children this had medical and emotional implications, the clinical picture of the mutations was completely different. The boy was reared as a girl based on his female phenotype, whereas in the girl the increased gonadotrophin levels gave rise to formation of ovarian cysts, which necessitated permanent suppression of pituitary secretion of LH and FSH. At present, these patients with GnRH analogues can be treated and their ovaries preserved.

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References

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