Familial clustering of impaired spermatogenesis: no evidence for a common genetic inheritance pattern

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BACKGROUND: The aetiology of impaired spermatogenesis is unknown in the majority of cases. Evidence of a contribution of genetic factors is still scarce. Therefore, the aim of our study was to assess whether male factor subfertility due to impaired spermatogenesis has a familial component and to test different genetic models of inheritance. METHODS: Cases were all men with severe idiopathic impaired spermatogenesis attending our fertility clinic from January 1998 until December 2001. Controls were all men with normozoospermia attending our fertility clinic in the same period. Family data were collected from the medical records and by additional interviews of the probands. If subfertility of a first-degree relative was mentioned, permission was sought to contact the affected family member in order to obtain all medical information available, including the results of semen analyses. RESULTS: In total, 160 patients and 285 controls were included in the analysis. Family size and number of brothers and sisters were equally distributed in both groups. In the patient group, 1.63% of the brothers who had tried to father a child were mentioned to be subfertile compared to 5.8% in the control group [odds ratio 3.18 (95% confidence interval 1.59–6.37)]. The subfertility among the brothers in the patient group was more often due to reduced semen parameters compared to the control group. The data did not fit with frequent autosomal dominant or recessive segregation. CONCLUSION: Male factor subfertility due to impaired spermatogenesis appears to cluster in families. Our data suggests that heritable genetic factors play a role in a limited number of cases. Impaired spermatogenesis is not caused by a common genetic defect, but is most likely a complex disease in which several different factors play a role.

Key words: familial clustering/impaired spermatogenesis/male subfertility

Introduction

Subfertility, defined as 1 year of unprotected intercourse without conception, affects 10–15% of couples (Hull et al., 1985; De Kretser, 1997; Snick et al., 1997; Evers, 2002). According to the World Health Organization (1987), in 47% of these couples semen parameters are decreased. In most cases, the cause of the reduced sperm quality is not known. In particular, little is known about the genetic aetiology of impaired spermatogenesis. Numerical chromosomal abnormalities are found by cytogenetic studies in ~4% of men with azoospermia (Tuerlings et al., 1998; Hargreave, 2000; Dohle et al., 2002). Structural chromosomal abnormalities include deletions of the Y chromosome, which have been found in another 6–13% of patients (Reijo et al., 1995, 1996; Kremer et al., 1997; Kuroda-Kawaguchi et al., 2001). However, in the vast majority of cases the aetiology of impaired spermatogenesis remains unknown and is classified as idiopathic (Snick et al., 1997).

To date, the only therapeutic option for couples with subfertility due to severely decreased sperm count is controlled ovarian hyperstimulation and follicle aspiration followed by ICSI. The therapeutic efficacy of ICSI is generally accepted, but there is still concern about potential transmission of genetic defects to the offspring (Bowen et al., 1998; Johnson et al., 1998; Meschede et al., 1998; te Velde et al., 1998). Although major birth defects seem not to be increased in children born after ICSI (Palermo et al., 1996; Sutcliffe et al., 2001; Bonduelle et al., 2002), Y chromosome deletions are transmitted to sons by ICSI and therefore they are likely to be infertile as adults (Page et al., 1999). If idiopathic impaired spermatogenesis is due to a heritable genetic factor, ICSI would be a suitable treatment option.
spermatogenesis would appear to be a genetic condition, then other unknown genetic abnormalities might also be transmitted via ICSI with a possible negative impact on fertility.

There is some evidence available for a genetic basis of male subfertility in humans, but this is still scarce. So far, several families with multiple subfertile male family members have been described in which a genetic defect segregates in the family (Chaganti and German, 1979; Leonard et al., 1979; Shabtai et al., 1980; Cantu et al., 1981; Rivera et al., 1984; Meschede et al., 1994; Chang et al., 1999; Saut et al., 2000; Rolf et al., 2002; Tuerlings et al., 2002; Gianotten et al., 2003). In addition, familial clustering of male subfertility has been observed in a case control study, which could be explained by an autosomal recessive mode of inheritance in the majority of cases (Lilford et al., 1994). Conclusions were based on a significantly increased number of subfertile brothers of men with reduced sperm counts as compared to fertile controls. These findings are supported by a study describing that men with an ICSI indication have fewer siblings than fertile controls (Meschede et al., 2000).

The fertility status of a couple, however, is not exclusively based on semen parameters as several additional factors of both partners contribute to the subfertile phenotype. In both studies demonstrating clustering of male subfertility, the patient group consisted of men with a very broad range of semen parameters. Both control groups consisted of fertile men of whom no semen parameters were available (Lilford et al., 1994; Meschede et al., 2000). In this study we focussed on severe impaired spermatogenesis, in order to avoid conflating male and female factors. Comparisons were made with a group of subfertile men attending the same outpatient clinic, who had normal semen parameters.

The aim of our study was to assess whether male factor subfertility due to impaired spermatogenesis has a familial component and to test different genetic models of inheritance. Therefore, we determined the prevalence of subfertility among relatives of patients with severe idiopathic impaired spermatogenesis and the prevalence of subfertility among relatives of patients with normal semen parameters. In addition, we determined whether the subfertility of the brothers was due to reduced semen parameters or caused by other factors.

**Methods**

**Patients**

Cases were all men with idiopathic azoospermia or extremely severe oligozoospermia who attended the Center for Reproductive Medicine of the Academic Medical Center from January 1998 until December 2001 with subfertility for at least 1 year. Oligozoospermia was defined as a total sperm count $<20 \times 10^6$ spermatozoa, in two consecutive semen samples. Semen analyses were performed according to the criteria of the World Health Organization (1992). Patients with a history of alcohol abuse, orchitis, surgery of the vasa deferentia, bilateral orchidectomy, chemo- or radiotherapy, obstructive azoospermia (confirmed by testicular biopsy), congenital bilateral absence of vasa deferentia, and patients with numerical and structural chromosomal abnormalities or deletions of the Y chromosome were excluded.

Controls were all men with subfertility for at least 1 year, attending the Center for Reproductive Medicine of the Academic Medical Center in the same period, who had normal sperm counts. Normozoospermia was defined as a total sperm count of at least $40 \times 10^6$ spermatozoa with a progressive motility and normal morphology of at least 40%, in two consecutive semen samples. The study was approved by the Institutional Review Board of the Academic Medical Center.

**Family data**

Of all cases as well as of all controls, family data were collected from the medical records. The number of brothers and sisters, the number of their children, and whether they had been conceived spontaneously was recorded. In cases of childless brothers or sisters, it was registered whether they had a regular sexual partner and whether the childlessness was voluntary or involuntary.

Relatives were considered to be subfertile when there was no pregnancy after 1 year of unprotected intercourse or when they had a child after assisted reproductive therapy.

If the information in the medical record was not sufficient, the probands were interviewed by telephone. If subfertility of a first-degree relative was mentioned, permission was sought through the proband to contact the affected family member in order to obtain all medical information available about his or her fertility status, including the results of semen analyses.

Adopted siblings, stepbrothers and sisters, and half-brothers and half-sisters were excluded from this study.

**Statistics**

The age of the patients and controls was compared using Student’s $t$-test and family size frequencies between patients and controls and were compared using Fisher’s exact test. All other comparisons between cases and controls were performed using logistic regression and results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Relatives without a partner and relatives with partner who were voluntarily childless were considered not to be at risk for subfertility. Therefore, only brothers who fathered at least one child, spontaneously or after fertility treatment, and brothers with a partner who were involuntarily childless were included in the analysis.

The consistency of the number of affected brothers of patients with idiopathic impaired spermatogenesis and their distribution within families was tested by segregation analysis. The observed frequency of subfertility among brothers of patients (number of affected brothers/total number of brothers at risk) was compared with frequencies expected under three genetic models assuming independence between the brothers of a patient and a low frequency of the disease allele. Only patients who did have at least one brother at risk for subfertility were included in the segregation analysis.

Model 1 assumed a single autosomal dominant allele (D) at the disease locus, resulting in a probability of 0.5 that a brother at risk is affected (Dd mating). Model 2 assumed a single autosomal recessive allele (d) at the disease locus, resulting in a probability of 0.25 that a brother at risk is affected (dd mating). Model 3 assumed a mixed genetic (one autosomal recessive allele) and environmental (other factors) model, in which the percentage of affected brothers due to a recessive gene and the population prevalence of the environmental factors causing subfertility were variable.
Results

Cases and controls

In total, 1701 couples visited the Centre for Reproductive Medicine of the Academic Medical Centre in the period from January 1998 until December 2001 because of subfertility for at least 1 year. Of these couples, 173 men (10.2%) had total sperm counts <2·10^6, without a known cause. They were all included in this study as patients. Another 323 men (19.0%) had total sperm counts >4·10^6 with a progressive motility and normal morphology of at least 40%. Those men were all included as controls.

Of 49 (28.3%) patients in the ‘patient’ group and of 68 (21.0%) men in the control group, data were not sufficiently recorded in the medical records and an additional telephone call was required. After follow-up by telephone, all required data were available for 160 (92.5%) cases and 285 (88.2%) controls. For the remaining cases and controls it was not possible to obtain further information and they were excluded from the analysis.

The mean ages of the patients and controls were 35.8 and 34.7 years, respectively (P = 0.06). In the patient group, 46 (29%) patients were azoospermic, 48 (30%) had a total sperm count <2·10^6, and 11 (7%) had a total sperm count of 2·5·10^6. 18 (11%) of 5–10·10^6 and 37 (23%) of 10–20·10^6. Of all patients, the medical history revealed 18 (11%) cases with orchidopexy, five (3%) with embolization of the v. spermatica and 11 (7%) with surgery of a hernia inguinalis. Testicular volume was reduced (<15 ml) in 102 (64%) patients and FSH was elevated (>7 IU/l) in 93 (58%) of patients.

Number of siblings with and without children

The total number of brothers and sisters and the number of brothers and sisters with and without children are shown in Table I. The 160 patients included in the analysis had 434 siblings: 216 brothers and 218 sisters. The 285 controls had 729 siblings: 354 brothers and 375 sisters. Family size expressed as the number of brothers or sisters per proband was equally distributed in the patient group compared to the control group (P = 0.435 and P = 0.515, respectively).

In the patient group, 52 (24%) brothers and 38 (17%) sisters were childless, but did not have a regular sexual partner, compared to 86 (24%) brothers and 54 (14%) sisters in the control group. Another 17 (8%) brothers and 21 (10%) sisters in the patient group had a regular partner, but had no wishes to have children, compared to 26 (7%) brothers and 34 (9%) sisters in the control group. These differences were not statistically different.

In the patient group, 126 (58%) brothers fathered one or more children, compared to 235 (67%) brothers in the control group. They conceived a total of 302 children (an average of 2.4) and 585 children (an average of 2.5), respectively. In the patient group, 151 (69%) sisters had at least one child compared to 281 (75%) sisters in the control group. They conceived 371 (an average of 2.5) and 713 (an average of 2.5) children, respectively. These differences were not statistically different.

The remaining 21 (10%) brothers in the patient group and the remaining seven (2%) brothers in the control group did have a regular partner, and mentioned that they were involuntarily childless. The remaining eight (4%) sisters in the patient group and the remaining six (2%) sisters in the control group were involuntarily childless with a regular partner.

Subfertility among brothers

The number of subfertile brothers among the brothers at risk for subfertility is shown in Table II. The 126 (58%) brothers in the patient group and 235 (67%) brothers in the control group who conceived at least one child were subfertile.

Table I. Number of siblings with and without children of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Patient group (N = 160)</th>
<th>Control group (N = 285)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Brothers (N = 216)</td>
<td>Sisters (N = 218)</td>
</tr>
<tr>
<td>Sibs with no children and no partner</td>
<td>52 (24%)</td>
<td>38 (17%)</td>
</tr>
<tr>
<td>Sibs with partner, voluntary childless</td>
<td>17 (8%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Sibs with child(ren)</td>
<td>126 (58%)</td>
<td>151 (69%)</td>
</tr>
<tr>
<td>Sibs with partner, involuntarily childless</td>
<td>21 (10%)</td>
<td>8 (4%)</td>
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</table>

Table II. Number of subfertile siblings among siblings at risk for subfertility

<table>
<thead>
<tr>
<th></th>
<th>Patient group (N = 160)</th>
<th>Control group (N = 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brothers (N = 147)</td>
<td>Sisters (N = 159)</td>
</tr>
<tr>
<td>Involuntarily childless with partner</td>
<td>21 (14.3%)</td>
<td>8 (5.0%)</td>
</tr>
<tr>
<td>Children after fertility treatment</td>
<td>3 (2%)</td>
<td>6 (3.8%)</td>
</tr>
<tr>
<td>Children after &gt;1 year</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>24 (16.3%)</td>
<td>15 (9.4%)</td>
</tr>
</tbody>
</table>
the patient group and seven (2%) brothers in the control group who were involuntarily childless with a regular partner tried to conceive a child and therefore had been at risk for subfertility. Thus, in total, 147 (68%) brothers in the patient group and 242 (68%) brothers in the control group were considered to be at risk for subfertility [OR 0.99 (95% CI 0.67–1.44)].

In addition to the 21 brothers in the patient group and the seven brothers in the control group who were involuntarily childless, three brothers in the patient group and four brothers in the control group conceived at least one child after fertility treatment. None of the brothers in the patient group and three brothers in the control group conceived a child after >1 year. Thus, in total, 24 (16.3%) of the brothers at risk in the patient group and 14 (5.8%) of the brothers at risk in the control group were reported to be subfertile, which was significantly different [OR 3.18 (95% CI 1.59–6.37)].

Four patients had two brothers with fertility problems, but none of the controls had more than one subfertile brother. Consequently, 12.5% of the patients reported at least one subfertile brother, which is significantly more than the 4.9% of the controls [OR 2.76 (95% CI 1.36–5.64)].

**Semen parameters of subfertile brothers**

In the patient group, results of semen analyses of the subfertile brothers could be obtained in 58% of subfertile brothers (Table III). Of the subfertile brothers, 42% had reduced semen parameters and 16% had normal semen parameters. No information about sperm quality could be obtained from 42% of the subfertile brothers, either because they had not visited a fertility doctor, they did not want to discuss the reason of subfertility with their brother or they reported a known female factor, but no semen analysis was performed.

In the control group, none of the subfertile brothers had reduced semen parameters and 36% had normal semen parameters. No semen analyses were available for 57% and no semen analysis was in 7% performed because of a known female factor.

**Subfertility among sisters**

The number of subfertile sisters among the sisters at risk for subfertility is shown in Table II. In total, 159 (73%) sisters in the patient group and 287 (77%) sisters in the control group were considered to be at risk for subfertility [OR 0.83 (95% CI 0.55–1.23)].

In addition to the eight sisters in the patient group and the six sisters in the control group who were involuntarily childless, six sisters in the patient group and five sisters in the control group had at least one child after fertility treatment. One sister in the patient group and three sisters in the control group conceived a child after >1 year. Thus, in total, 15 (9.4%) of the sisters at risk in the patient group and 14 (4.8%) of the sisters at risk in the control group were reported to be subfertile [OR 2.03 (95% CI 0.90–4.60)]. None of the patients and controls had more than one subfertile sister.

Information about the cause of the subfertility was available for 40% of the subfertile sisters in the patient group and for 28% of the subfertile sisters in the control group (Table IV).

### Table III. Reason of subfertility among brothers of cases and controls

<table>
<thead>
<tr>
<th>Reason of Subfertility</th>
<th>Patient group brothers (N = 24)</th>
<th>Control group brothers (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoo/oligozoospermia</td>
<td>10 (42%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normozoospermia</td>
<td>4 (16%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>Female factor</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (38%)</td>
<td>8 (57%)</td>
</tr>
</tbody>
</table>

### Table IV. Reason of subfertility among sisters of cases and controls

<table>
<thead>
<tr>
<th>Reason of Subfertility</th>
<th>Patient group sisters (N = 15)</th>
<th>Control group sisters (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female factor</td>
<td>3 (20%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Azoo/oligozoospermia of partner</td>
<td>2 (13%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Unexplained</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (60%)</td>
<td>10 (72%)</td>
</tr>
</tbody>
</table>

### Segregation analysis

In the patient group, the observed prevalence of subfertility among brothers at risk was 16.3% (95% CI 11.2–23.1, lnL = 65.42). Both the autosomal dominant (lnL = -101.89) and the recessive (lnL = -65.66) model were rejected (P < 0.0001 and P = 0.011, respectively).

When assuming a mixed autosomal recessive and environmental factors model, the model best fitting the observed data was a model in which 47% of the subfertility among the brothers of the patients is caused by an autosomal recessive gene, whereas the remaining 53% is caused by other factors with a population prevalence of 8.7%.

When assuming a mixed autosomal dominant and environmental factors model, the model best fitting the observed data was a model in which 23% of the subfertility among the brothers of the patients is caused by an autosomal dominant gene, whereas the remaining 77% is caused by other factors with a population prevalence of 6.4%.

### Discussion

In this study, subfertile men with idiopathic azoo- or severe oligozoospermia reported significantly more often subfertility among their brothers compared to subfertile men with normozoospermia. In addition, the subfertile brothers in the patient group had reduced semen parameters more often than the subfertile brothers in the control group. These findings indicate that male subfertility due to impaired spermatogenesis clusters in families.

As we collected the family data via the probands, who are probably not always aware of fertility problems among their relatives, reporting bias might have influenced our results. It is reasonable to assume that patients suffering of subfertility are more often aware of fertility problems in their family than controls. This was one of the problems mentioned in the case control study performed earlier as the control group consisted of subfertile sisters.
of fertile men attending vasectomy clinics or a maternity department (Lilford et al., 1994). Among those controls, no subfertile brothers were mentioned at all, which is very suggestive of reporting bias.

In our study, we focussed on men with the most severely abnormal sperm counts and therefore we could identify a control group within the subfertile population. This has the advantage over the previous study of reducing any bias, which may result from greater propensities for information about fertility to be declared when the proband is childless, than when he has children. Use of subfertile controls is conservative, because the measured influence of any familial clustering would be diluted if some other causes of infertility also had a familial component. Nevertheless, this method should provide an unbiased estimate of the difference in clustering between subfertile men with impaired spermatogenesis and those with normal semen variables. Indeed, no substantial differences in number of subfertile sisters were mentioned between the cases and the controls, which argues against significant differences in reporting bias between both groups.

The prevalence of familial subfertility found in this study, however, might be underestimated in both groups due to unawareness of subfertility among relatives by the proband. Moreover, not all relatives had tried to conceive a pregnancy and thus were not yet at risk for subfertility. Among those relatives, there might be some subfertile brothers and sisters that are not detected as affected in this study. If there are genetic factors involved in impaired spermatogenesis, this effect might be bigger in the patient group than in the control group, resulting in understimation of the genetic component. Therefore, we determined the prevalence of subfertile brothers only among those brothers who already tried to father a child.

As other factors than reduced semen parameters might be the cause of the subfertility among brothers, the clustering found in this study is not only due to subfertility caused by sperm defects. Thus, subfertility due to impaired spermatogenesis accounts only for a part of the clustering found, which is therefore overestimated. As we were informed about the semen parameters of most subfertile brothers, we indeed know for sure that some brothers were subfertile for reasons other than reduced sperm counts.

Unfortunately, semen analyses were not available of all brothers who were reported to be subfertile, either because they had not yet visited a fertility clinic or because they did not want to discuss the reason for their subfertility. However, we found a high proportion of severely abnormal sperm counts among brothers of subfertile men with azoospermia, which is probably higher than in the control group. This could be the result of some sort of interaction between severity of test result, willingness to disclose it and status of brother triggering the request. This does not seem very plausible to us, but remains a theoretical possibility.

Despite the possible under- or overestimation of the prevalence of subfertility, we confirmed the statistically significant increased probability of a subfertile brother among subfertile men than among controls as was found before by Lilford et al. (1994). While confirming the tendency of subfertility due to reduced semen parameters to cluster in families, the strength of the association was lower in the current study. This is surprising, because we chose a more severely abnormal phenotype where intuitively one might suspect a higher proportion of genetic cases. Therefore, the familial occurrence of subfertility due to impaired spermatogenesis might also be caused by non-genetic factors like shared environment.

A common genetic factor affecting reproductive fitness might seem oxymoronic at first sight. However, in cases of autosomal recessive single gene defects, only homozygotes are affected and recessive males would not be subfertile, but pass the defect to their children. An autosomal dominant defect of the maternal allele or an aberration of the X chromosome could also explain how male subfertility can be transmitted to the next generation.

Several families with multiple subfertile male family members have been described suggesting a genetic origin of male subfertility (Chaganti and German, 1979; Leonard et al., 1979; Shabtai et al., 1980; Cantu et al., 1981; Rivera et al., 1984; Meschede et al., 1994; Chang et al., 1999; Saut et al., 2000; Rolf et al., 2002; Tuerlings et al., 2002; Gianotten et al., 2003). In two families, an autosomal recessive mode of inheritance was suggested, but no cause for the shared infertility could be identified (Chaganti and German, 1979; Cantu et al., 1981). In four families, structural chromosomal abnormalities were found (Leonard et al., 1979; Shabtai et al., 1980; Rivera et al., 1984; Meschede et al., 1994) and in four families, a microdeletion of the Y chromosome was transmitted from the father to his infertile sons spontaneously (Chang et al., 1999; Saut et al., 2000; Rolf et al., 2002; Gianotten et al., 2003). In a recent case, report an autosomal dominant trait of male subfertility with sex-limited expression was suspected by segregation analysis (Tuerlings et al., 2002).

In the previous study performed by Lilford et al., an autosomal recessive mode of inheritance was suggested in 60% of the cases. The data found in our study also do not fit with an autosomal recessive model for the total population. Assuming a mixed model, 47% of the subfertility might be due to an autosomal recessive gene, whereas the remaining 53% is caused by other factors. However, the results of the segregation analysis also might be underestimated by unawareness of familial subfertility by the proband, which also might have influenced the results of Lilford et al. (1994).

Our data suggests that male subfertility due to impaired spermatogenesis is familial, but only in a limited number of the cases. A proportion of these genetic cases could be caused by an autosomal recessive single gene defect, but autosomal dominant gene defects, inherited from the mother, might theoretically also play a role in a limited number of cases. In the majority of cases, however, the subfertility phenotype is not segregating in the family. Subfertility in these cases might, therefore, be due to environmental factors, but also de novo mutations in several different genes might play a role.

Population-based genetic studies would be indicated to map the locus involved in impaired spermatogenesis if the majority of cases are all due to one gene which segregates in families. However, this is unlikely because we did not find a common inheritance pattern in our population. In addition, the gene
would have to be very common in order to appear so frequently in homozygous form and spermatogenesis is such a complicated process that it would be surprising if only one gene was involved in such a common condition.

All together, we can conclude that the aetiology of impaired spermatogenesis resulting in male subfertility is not caused by a common genetic defect, but is most likely a complex disease, in which several different factors play a role.

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