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Paternity in men with cystic fibrosis: A retrospective survey in France☆

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Abstract

Background: Because more patients reach adulthood, new questions as "what about having a child and/or paternity responsibility?" arose.
Method: We performed a retrospective investigation based on the French CF registry. The context of the paternity and the health status of fathers were recorded. A comparison with clinical status of non-father patients and a compilation of follow-up data to evaluate its impact were done.
Results: Forty-eight men had 69 children. One fourth was said to be natural conceptions, 69% needed assisted reproduction techniques. No child had CF. Clinical status of men was satisfactory: mean BMI was 20.9 kg/m^2 and mean FEV_1 and FVC were 50.5% and 69.2% of predicted, respectively. When matched to CF non-fathers, few significant differences appeared. More non-fathers were F508del/F508del ($p=0.03$). Fathers' sputum cultures were positive for non-*Pseudomonas aeruginosa* strain ($p=0.05$), including *Staphylococcus aureus* ($p=0.01$). Mean age at diagnosis was higher, and based on minor evidence of sterility as first symptom leading to the diagnosis of CF ($p=0.01$) or aspergillosis ($p=0.03$). The 3-year follow-up showed no degradation of the clinical status.
Conclusion: Men having paternity responsibility over children did not differ from the CF male population and neither did it seem to have an impact on the disease course.

Keywords: Cystic fibrosis; Paternity; Clinical status; Clinical impact

1. Introduction

Cystic fibrosis (CF) is the most common life-limiting genetic disorder in white Caucasians. It is due to a defect in the cystic fibrosis gene encoding for cystic fibrosis conductance regulator (CFTR) protein. It leads to a chronic bronchial infection and obstructive pulmonary disease associated with various extra-respiratory symptoms as pancreatic insufficiency, distal intestinal obstructive syndrome, liver cirrhosis, diabetes and others.

The combination of early diagnosis and adjusted care management had led to higher life expectancy. Thus, more and more CF patients reach adulthood. In France, the mean age of patients was 12.2 years in 1994 (median: 11 years), whereas it was 15.5 years in 2002 (median: 14 years). Moreover, mean life expectancy at birth was 38.8 years for the 1999–2001 period [1,2]. In 1994, 20.8% of the registered patients in the French CF registry were 18 years old and over vs. more than one third (37.1%) in 2002 [1,2].

Because of this increasing male adult population, new questions have to be faced. Two of these are "what about having a child and/or paternity responsibility?" and "what is

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the impact of the paternity responsibility on the disease course and management?" Almost 98% of CF males patients are infertile [3]. This infertility is the consequence of congenital bilateral absence of the vas deferens (CBAVD) and/or of absence of seminal vesicles; therefore, spermatozoa cannot be ejaculated [4,5]. Indeed, CFTR mutations may interfere at an early embryonic stage, when the Wolfian duct is differentiated into the scrotal vas and distal epididymis. The lack of secretion may lead to the interruption of the development and agenesis of the deferens [6]. These hypotheses are coherent with observations reported on adults and children [4,7].

Male infertility may be a clue to diagnose CF in adults, using a semen analysis to establish their fertility status [8]. On the other hand, CBAVD may also be associated with infertility in males without classical CF. One CFTR gene mutation and/or variant and a positive sweat test can be found [9–11]. This physiopathology was not considered in the present study. Assisted reproductive techniques (ART) allow men with CF to have children despite effective infertility.

For many years artificial insemination with a sperm donor (AID) was the only alternative to men infertility. Since the beginning of the 1990s, in vitro fertilisation using microsurgical sperm aspiration coupled with intra-cytoplasmic spermatozoan injection (ICSI) offers a new opportunity to have a child [12].

2. Materials and methods

Since 1992, the French CF registry has collected and analysed data from most of the CF patients regularly seen in CF care centres in France. It is based on a yearly questionnaire collecting demographic, clinical and social data for every CF patient seen during that period. Consent from the patients, or from the parents if minor, to perform analyses with the collected data was obtained when the patient was first integrated in the registry. Thematic questionnaires have been implemented, as tools to study specific aspects of CF (pregnancies, *Burkholderia cepacia*, etc.).

The thematic database on paternity was established in 2003. Data are requested on men's birth date, date at diagnosis, genotype, date of death, if applicable. Modalities of the paternities were also registered: natural conception (NC), artificial insemination with a sperm donor (AID), intra-cytoplasmic spermatozoan injection (ICSI), or adoption (AD). Genetic counselling prior to the conception was recorded. Data on each child (date of birth, sex, having CF or not, single or twin birth) were also asked.

Previous to continuous recording on paternities, we performed a retrospective study. All participating CF centres to the French CF registry were asked to notify, using the same questionnaire, all men who had had a child, whatever the year of birth and the modality of paternity.

The health status of the fathers who attended a CF centre in 2002 was evaluated using the yearly collected data from the French CF registry. Variables included were BMI expressed as kg/m^2, and FVC, FEV_1 as % of predicted value. Measures from those who died or received transplantation were excluded. Results of sputum cultures were gathered into two categories: "*Pseudomonas aeruginosa* family" (including *P. aeruginosa*, *Stenotrophomonas maltophilia*, *B. cepacia*), and "non-*P. aeruginosa* family" (including *Haemophilus influenzae*, *Staphylococcus aureus*, *Aspergillus*, and *Candida*). Occurrence of liver cirrhosis, diabetes and treatment (IV-ATB), mean number of courses for those having at least one enzymatic supplementation as indicator of pancreatic insufficiency were also taken into account. Those fathers attending were compared to non-father CF patients. We matched one father to two non-fathers, in order to measure differences that might exist within a "medium" population. It was composed of males without a child, of similar age (S.D. = 2 years), having a fully identified genotype, and attending, at least for the youngest adults, the same CF care network. This criterion was not used for patients over 33 years in 2002, because of the small size of the CF population. Indeed, in the 2002 enquiry, only 323 males could be possible pairs, but only 78 were 33 years or older [2]. Moreover, few centres managed old patients and practitioners tended to have similar policies.

Extracted variables were similar to those previously considered. We added evidence leading to diagnosis (meconium ileus, malnutrition, diarrhoea, respiratory problems, nasal polyposis, and sterility as first symptom leading to the diagnosis of CF). Genotypes were divided into 6 groups (F508del/F508del, F508del/other, F508del/unknown, other/other, other/unknown and unknown/unknown). They were also classified according to the disease expression: severe (2 severe mutations), mild (severe/mild or mild/mild), or unknown (at least one unknown mutation, or mutation for which expression was not measurable). The pancreatic status was elected as the classification criterion.

Finally, we compiled a 3-year follow-up data to measure the impact of the presence of a child at home on the clinical status. The follow-up was carried out during 3 years for children born in 1999 or 2000, 2 years for those born in 2001, and 1 year for these born in 2002. Selected data were BMI, FEV_1 and FVC, results of sputum cultures, as previously described. Frequency of outpatient visits, daily hospitalisations, IV-ATB treatment, enzymatic supplementation, and liver cirrhosis, diabetes, transplantation or death were also registered.

3. Analysis

Continuous data were presented as means with the indication of standard deviation (S.D.) and median value. Comparisons were performed using a two-tailed *t*-test for continuous variables. Categorical variables were presented as the number of positive events. They were compared using

the chi-square test or, for small-size samples, the Fisher exact test. A significant level of $p \leq 0.05$ was selected. Computer software Epi Info 6.04 was used for all analyses.

4. Results

Eighty-three centres were contacted. All CF care centres having patients over 18 years ($n=71$) participated to the present study, including the most important ones. Only 12 of them (17%) reported men having children.

Sixty-nine paternities were recorded for 48 men (Table 1). Only 3 births occurring in the 1960–1969 and 1970–1979 periods, respectively (0.3 per year meanly), have been reported. Thirteen occurred in the 1980s (1.3 yearly) and 28 in the 1990s (2.9 per year). Between 2000 and 2003, 22 births have been notified (5.5 yearly). Fathers were meanly aged of 37.7 years, and their mean age at diagnosis was 19.7 years. For 13 men, diagnosis occurred when their 24 children were meanly aged of 8.9 years. In 2003, 6 men (12.5%) were dead (mean age 41.3 years); thus, 8 children became fatherless at the mean age of 10.2 years.

One fourth of the paternities ($n=18$) was said to be natural conception ones, 35% ($n=24$) had required AID, 34% ($n=23$) needed ICSI, and 6% ($n=4$) were adoptions. Paternities registered in the 1960s or 1970s were natural or AID conceptions. Adoption was first mentioned in the late 1980s, whereas ICSI was first used in the late 1990s. Since 1995, 23 ICSI have been performed, including 8 during the 1990s and 15 in the 2000–2003 period (Fig. 1).

Table 1
Clinical description of CF men having children

Fathers (number)	48
Mean age ± S.D. (years)	37.7 ± 8.2
Mean age at diagnosis ± S.D. (years)	19.7 ± 17.8
Alive in 2003 (number) [%]	42 [87.5%]
F508del/F508del (number) [%]	13 [27.1%]
Severe genotype (severe/severe) (number) [%]	24 [50.0%]
Mild genotype (severe/mild or mild/mild) (number) [%]	11 [22.9%]
Unknown severity (at least one unknown mutation) (number) [%]	13 [27.1%]
Natural conception (number) [%]	18 [26.1%]
AID conception (number) [%]	24 [34.8%]
ICSI conception (number) [%]	23 [33.3%]
Adoption (number) [%]	4 [5.8%]
Modalities of conception	
F508del/F508del (natural/AID/ICSI/adoption)	1/2/8/2
Severe genotype (natural/AID/ICSI/adoption)	3/8/11/2
Mild genotype (natural/AID/ICSI/adoption)	2/5/3/1
Unknown severity (natural/AID/ICSI/adoption)	4/3/5/1
Age at first birth ± S.D. (years)	30.7 ± 5.2
Children (number)	69
Females [%]	59
Males [%]	39
Twin pairs (number)	7

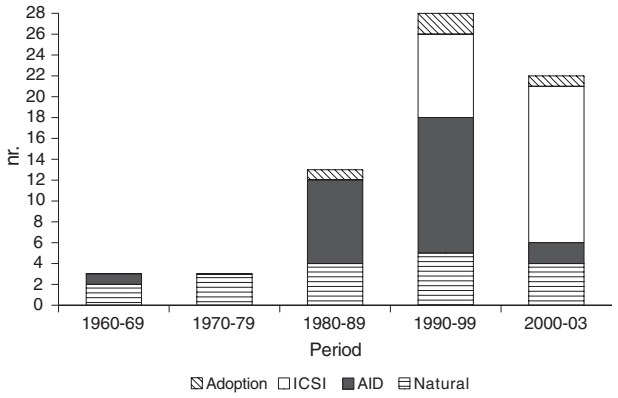

Fig. 1. Distribution of the number of births registered by period and mode of procreation.

Thirteen men were F508del homozygotes and 21 compound heterozygotes F508del/other mutation. Ten F508del/F508del used AID or ICSI and only one fathered naturally. Only 4 F508del/other mutation fathered naturally; they carried R117H, G542X, E60X and 2789+5G→A alleles. Twenty-four patients had a severe disease expression genotype, according to pancreatic status. Eleven had a mild genotype and 13 a non-classified genotype.

Only one natural conception over 13 was reported from a F508del/F508del father, whereas 10 required AID or ICSI (76.9%). Men bearing a severe disease expression genotype had few natural conceptions (3/24, i.e., 12.5%), whereas those having mild or unknown genotype had, respectively, 2/11 (18.2%) and 4/13 (30.8%) naturally fathered. On the other hand, the frequency of use of ART decrease with the degree of disease severity: 11 of the 24 men with severe genotype (79.2%), but only 8 of the 11 with mild one, and 8 of those with unknown expression (61.5%) required it.

The mean age at the first naturally conceived birth was 28.1 years (S.D.=6.1), whereas it was 31.3 years (S.D.=4.9) when ICSI was required. Men choosing adoption were even older: 37.8 years (S.D.=7.1). Whatever the modality of conception, 33 men had only one child, 13 had 2 and 4 had 3. Each CF patient had 2 children when conceived naturally. One man had meanly 1.5, 1.2, and 1.0 children using AID, ICSI, and AD, respectively. The medium-size family was 1.4 children.

Fifty-two percent of the CF men received genetic counselling. No child had CF. Twenty percent of births ($n=14$) were twins. One pair of twins has been NC conceived, 2 through AID and 4 via ICSI. Three of them were single-sex pairs.

Forty of the 48 men having responsibility over children attended a CF care centre in 2002. Six were dead, 1 was lost to follow-up, and 1 moved to North America. The mean age of those seen in 2002 was 37.7 years (S.D.=1.5), the median value was 36.0 years. Their mean age at diagnosis was 19.1 years (S.D.=18.8), and half of them were diagnosed before the age of 10. Their mean BMI was 20.9 kg/m^2 (S.D.=3.05), even if 7 of them had value below

18.5 kg/m^2. The median value was 20.5 kg/m^2. Mean FEV_1 and FVC were, respectively, 50.5% and 69.2% of predicted values (median 48.5% and 69.7% of expected), excluding those who died or were transplanted. Four men had a FVC below 30% predicted, 2 of them died in 2002. Thirteen men had an FEV_1 below 30% expected, including those 2 who died and one enrolled on a waiting list for lung transplant. Twenty-six fathers had at least one "*P. aeruginosa* family" strain, and 13 had also non-*Pseudomonas* strains in sputum cultures. Compilation of clinical events showed that none had liver cirrhosis, 18.4% had diabetes. IVATB courses were required for 22 of the 40 men with the mean number of courses being 1.95 per patient. Finally, 29 (72.5%) required pancreatic enzymatic supplementation.

Thirty-four fathers were matched to 68 non-fathers. The mean ages in 2002 were similar (35.7 years vs. 35.0). Results are summarised in Table 2. Mean age at time of diagnosis was 5 years higher (15.3 vs. 10.2 years NS) in the fathers group than in the childless one. No significant difference was observed in the occurrence of meconium ileus, diarrhoea, or respiratory disease, as evidence to diagnosis. Malnutrition was 2 times less frequent among the CF fathers than among their matched pairs (NS). On the other hand, men having fathered had about 6 times more frequently nasal polyposis (8.8% vs. 1.5% NS) and a greater propensity of being diagnosed during a consultation for difficulty to procreate ($p=0.012$). More F508del/F508del patients were identified in the non-father group than in the father one (26.4% vs. 48.5% $p=0.03$). Anthropometrical measurements showed no differences between both groups. Mean FVC and FEV_1, despite being slightly higher in the group of men with children, did not significantly vary. No significant difference in the frequency of occurrence of "*P. aeruginosa* family" strains was found, but it was in the "non-*P. aeruginosa*." Indeed, 83.8% of the CF male patients having at least one child had positive cultures but 64.5% of the childless men ($p=0.05$). The highest difference was observed in the occurrence of *S. aureus*: 64.5% of the fathers vs. only 37.1% of the non-fathers ($p=0.012$). Frequencies of liver cirrhosis and diabetes were similar in both groups. A significant difference was observed in the occurrence of aspergillosis: 25% of men with children vs. 8.8% of the non-fathers ($p=0.036$). IV-ATB treatment and pancreatic enzyme supplementation were required in both populations in similar proportions.

The 3-year follow-up showed no clinical deterioration during the period following the paternity. Mean BMI, FEV_1, and FVC remained stable, as well as the results of sputum cultures. Only the number of outpatient visits at the CF care centre increased from 2.9 to 4.5 per year (NS).

Table 2
Description and comparison of clinical data for men having children with matched-paired CF patients without children (NS=not statistically significant)

	Fathers (number)	Non-fathers (number)	*P*
Number	34	68	
Mean age in 2002±S.D. [median] (years)	35.67±7.44 [34.0]	34.99±7.50 [34.0]	NS
Range	[24.0–59.0]	[23.0–60.0]	
Mean age at diagnosis±S.D. [median](years)	15.32±16.08 [6.5]	10.17±13.95 [3.0]	NS
Clinical evidences			
Meconium ileus	2/34	1/66	NS
Malnutrition	4/34	17/66	NS
Diarrhoea	8/34	24/66	NS
Respiratory problems	18/34	39/66	NS
Sterility as symptom at diagnosis	7/34	3/66	0.012
F508del/F508del	9/34	33/68	0.033
Died	1	2	NS
Lung transplantation	1	1	NS
Enrolled on a waiting list in 2002	1	4	NS
BMI±S.D. (kg/m^2) [median][a]	21.16±2.94 [20.6]	20.81±3.49 [20.9]	NS
Range	[15.60–29.41]	[13.73–30.42]	
FEV_1±S.D. (% pred) [median][a]	50.24±26.91 [48.4]	47.11±26.85 [38.3]	NS
Range	[13.53–119.43]	[16.19–114.11]	
FVC±S.D. (% pred) [median][a]	69.47±24.79 [69.7]	64.70±22.67 [61.2]	NS
Range	[20.88–121.79]	[24.79–110.59]	
P. aeruginosa family strains (positive culture)	23/31	51/62	NS
Non-*P. aeruginosa* family strains (positive culture)	26/31	40/62	0.054
Including *S. aureus*	20/31	23/62	0.012
Liver cirrhosis	0/33	6/68	NS
Diabetes	7/33	17/68	NS
Aspergillosis	8/33	6/68	0.036
IV-ATB courses (nr)	19/34	40/68	NS
Mean number of courses±S.D.	2.06±1.60 (17)	2.43±1.45	NS
Pancreatic enzymatic supplementation	26/34	55/68	NS

[a] Excluding patients who died during the study or had received transplantation.

5. Discussion

We compiled data on 48 CF males having fathered before 2004. One fourth of the paternities was said to be natural conceptions, and 69% needed assistance to procreation. The mean age of the father at the time of the study was 37.7 years (S.D. = 8.2), and the mean age at first birth, whatever the modality of procreation, was 30.7 ± 5.2 years. Twenty-four had a severe disease expression genotype, and 11 a mild genotype.

The number of men registered as having children whatever the modality of procreation has increased since 1960. The number of natural conceptions or adoptions remained stable all over the studied period. Most of the procreations using ICSI occurred in the last 10 years and tended to substitute for AID (Fig. 1). Indeed, for many years, AID was the only alternative to male infertility. Since the beginning of the 1990s, in vitro fertilisation using microsurgical sperm aspiration coupled with ICSI offers a new opportunity to have a child for CF men. Hubert et al. [14] noticed that only 2 of the 25 men who asked for ART first chose AID, vs. 23 who chose ICSI. Of the 10 couples who had no child with ICSI, two chose AID as a second option [14].

The comparison between men having children and those without showed that both populations were closed. Nutritional and respiratory status of French adults were close to those calculated in the present study. Dray et al. measured in an adult population meanly aged of 28.8 years, a mean BMI equal to 19.1 kg/m^2 and that mean FVC was 61.9% of predicted (S.D. = 23.5) and 47.1% of predicted (S.D. = 25.5) for FEV_1.[13]. Another study performed on patients over 30 years, but diagnosed before the age of 5, found a mean BMI of 19.5 kg/m^2 in both groups, a mean FVC of 68% and 70%, respectively, and a mean FEV_1 being 49% and 54% [15].

Despite the overall "good" clinical status, we observed that 8 children became fatherless at a mean age of 10.2 years. A girl became fatherless at the age of 35.9 years. Her father carried the F508del/unknown genotype and was diagnosed at the age of 61.8 years, less that 1 year before dying. If excluding this particular case, the mean age of children when their fathers died is 6.1 years. The proportion of orphan in the registered population is over 10%. As a comparison, in France, in 1999, only 2.1% of the children were fatherless before the age of 21 years [16]. The relative risk of becoming fatherless when the father is CF is statistically increased (RR = 5.2, 95% CI: 2.4–11.2, $p < 0.0001$).

Few cases of natural fathering have been described in men having proven CF (Table 3). Of the 10 cases found in the literature, 2 were brothers (cases 2 and 3). All men but 2 (numbers 1 and 3) appeared to have a moderate form of pulmonary disease. Few men had gastrointestinal disease problems, including pancreatic insufficiency. All but numbers 9 and 10 had "positive" sweat tests. Diagnosis of CF of case number 10 can be discussed. Indeed, he had meconium ileus with a normal pancreatic function and a questionable genotype. In most cases, the mean age at diagnosis was higher than the mean age at birth. Six semen analyses were performed: 5 were normal, and 1 too thick. No man had paternity testing, only ABO and Rhesus typing were done with results consistent with paternity (numbers 4 and 6). Men numbers 8, 9 and 10 had CFTR gene analyses; results were also coherent for paternity, except for the third child of number 9, who carried no CFTR gene mutation [17–25].

In the present study, no data were available on the truthfulness of natural conceptions nor on the genetic status of the children's mothers.

Boyd et al. evaluated the fertility and pregnancy outcomes of men and women with cystic fibrosis within a large British cohort using the UK Cystic Fibrosis Database. Few individuals sought fertility treatment (1% men, 0.5% women) or achieved pregnancies (1.3% of partners of men, 5.7% women). They concluded that optimal adult

Table 3
Synthesis of case reports on paternity in men having CF

Case	Respiratory disease	Gastrointestinal disease	PI	Sweat test	Age at onset	Age at diagnosis	Age at birth	Sperm analysis	Number of children	Genotype	Reference
1	Severe	Severe	Yes	Positive	40 years	64 years			5		[18]
2	?	?	?	Positive		"Proven CF"			3		[17]
3	Classical[a]	Classical[a]	?	Positive		31 years[b]			4		[17]
4	Moderate	Yes	?	Positive	4 years	21 years	29 years	Normal	1		[19]
5		Severe	Yes	Positive		31 years[c]			1		[20]
6	Moderate	No	?	Positive	21 years	19 years	21 years	Normal	2		[22]
7	Mild	No	Yes?	Positive	30 years	32 years		Normal	1		[21]
8	Moderate	No	No	Positive		30 years		Thick	1	F508del/-	[23]
9	Severe	No	No	Normal	29 years	40 years	<30 years	Normal	2 or 3	3849+10 kbC>T homoz	[24]
10	Absence	No	No	Normal	Meconium ileus	36 years	35 years	Normal	1	F508del/-9t/7t	[25]

[a] Postmortem examination.
[b] Age at death.
[c] Died age unknown.

health should improve the reproductive prognosis for both men and women [26].

Fertility, infertility, practical and ethical aspects of ART and parenthood have to be approached and discussed with the patient and his partner by the whole care giving team. De Braekeleer et al. investigated the level of disease knowledge in adults and teenagers CF patients. More than 60% of teenagers and 86.2% of adult knew that male infertility could be a manifestation of CF. Surprisingly, only less than 10% of the nurses knew about it vs. 2/3 of the specialists practitioners or of the parents of CF children [27]. Sawyer et al. also reported reproductive knowledge and attitudes of CF males. Ninety percent of them knew that most of the CF males were infertile, and they first heard about it from the care provider during teenagers. They reported no more stress and accepted it as "part of CF," but only 1/3 had had semen analysis to establish their fertility status. Only 50% of the parents knew that CF males may be infertile, but only 1/10 thought they had enough knowledge to talk about it with their child [28]. Patients also reported that they were told too late about the link between CF and reduced fertility. They would have preferred to be informed at the age of 14 years ($p < 0.001$). They also expected more information on reproductive options and 85% planned to have children [29]. Finally, Fair et al. showed that CF adult patients confer a high importance on issues on fertility and parenting. Data were requested from patients, even if the subject appeared to be difficult, especially for them [30].

6. Conclusion

The present study offers a large complete clinical description of CF men having paternity responsibility over children. They did not significantly differ from the CF male population of similar age. Their clinical status was overall satisfactory and the presence of a child did not seem to have either a positive or a negative impact on the disease course and management. Considering that male infertility is an inevitable component of CF and that ART is available, the feasibility of having a child has to be discussed between the CF patients and the multidisciplinary CF team. However, the possible premature death and its consequence for the family have to be taken into account with the patient and his family according to his current clinical status.

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