Fertility status in male cystinosis patients treated with cysteamine

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Objective: To analyze the fertility status in adult, male cystinosis patients treated with cysteamine. Cystinosis is an autosomal recessive disease leading to intralysosomal cystine accumulation. Worldwide, a few female cystinosis patients have given birth. However, no male cystinosis patients are known to have induced pregnancy. Adequate cysteamine treatment might improve male fertility.

Patient(s): Seven male cystinosis patients (19–43 years) were submitted.

Intervention(s): Glomerular filtration rate was estimated using the Cockcroft formula. Serum LH, FSH, testosterone, and inhibin B were determined. Semen analysis was performed in five patients. Testicular biopsy was performed in one patient.

Results: Glomerular filtration rate ranged between 10 and 110 (normal >90) mL/min/1.73 m^2, LH and FSH levels ranged between 7.4 and 235.0 (normal 1.4–8.5) E/L and 6.8–298.0 (normal 1.5–11) E/L, respectively. Plasma testosterone level ranged between 8.7 and 31.3 (normal 11–45) nmol/L; plasma inhibin B level ranged between 10 and 210 (normal 150–400) ng/L. All of the collected sperm samples showed azoospermia. The testicular biopsy showed a Johnson score of 8 to 9.

Conclusion(s): We demonstrate azoospermia in male cystinosis patients, even if adequately treated with cysteamine starting from an early age. The finding of spermatogenesis in the testis biopsy of one patient may provide opportunities to male cystinosis patients to produce their own offspring by in vitro fertilization after testicular sperm extraction. (Fertil Steril® 2010;93:1880–3. ©2010 by American Society for Reproductive Medicine.)

Key Words: Cystinosis, infertility, azoospermia, cysteamine

Cystinosis is an autsosomal recessive disorder caused by mutations in the *CTNS* gene, resulting in a defect in the lysosomal cystine carrier, which leads to intralysosomal cystine accumulation in various tissues (1). It is treated by the administration of cysteamine, which removes cystine from the lysosomes. In the most frequent infantile form, cystinosis presents as proximal tubular damage called the renal Fanconi syndrome, which usually becomes clinically evident around 6 months of age. Renal failure in these patients progresses into end-stage renal disease around the age of 10 years (2).

After renal transplantation cystine continues to accumulate in extra-renal tissues, including the eyes, muscles, central nervous system, and various endocrine organs (2). Dysfunction of the thyroid gland and pancreas is common (3–5). Testicular function is also affected. Worldwide, a few female cystinosis patients have given birth. However, there are no male cystinosis patients known to have induced pregnancy (6). Adequate cysteamine treatment, in particular when started from early age, might improve male fertility. Furthermore, reproductive techniques like artificial insemination or in vitro fertilization (IVF) after, for example, testicular sperm extraction (TESE) might help to overcome these problems.

In renal disease in general, testicular function is mostly consistent with renal function. Male patients treated with dialysis show low testosterone levels, high and high-to-normal levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), respectively, and a poor sperm quality. After renal transplantation hormone levels mostly normalize and sperm quality generally improves, but remains subnormal (7). In patients with cystinosis, Chik et al. (6) showed that the effects of renal dysfunction and transplantation cannot explain the primary hypogonadism seen in adult male American patients not treated with cysteamine. A control group of male patients receiving similar immunosuppressive agents only showed minimally impaired testicular function compared with the cystinosis group.

Our aim is to analyze the fertility status of the adult, male, cystinosis population treated with cysteamine.

PATIENTS AND METHODS

Patients

After obtaining an informed consent form, seven male patients were included. They were between 19 and 43 years

Received September 19, 2008; revised December 27, 2008; accepted December 29, 2008; published online February 12, 2009.

M.T.T.B. has nothing to declare. J.A.M.K. has nothing to declare. M.C.H.J. has nothing to declare. E.N.L. has nothing to declare.

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0015-0282/10/$36.00
doi:10.1016/j.fertnstert.2008.12.113

of age. Cystinosis was diagnosed in early childhood by the measurement of elevated cystine levels in leucocytes, and was confirmed by mutation analysis of the *CTNS* gene in all patients. All patients were treated with cysteamine starting from the median age of 4 (range = 1.5–23) years, and treatment was regularly adapted according to leukocyte (white blood cell) cystine levels (before 2,001 in total white blood cell, and starting from 2,001 in polymorphonuclear leukocytes). Five patients were transplanted and had a functioning renal graft; one (patient 3) had a nonfunctional renal graft and was treated with hemodialysis, and one (patient 6) had preterminal renal failure. Two patients received androgen suppletion, which was stopped 3 months before the study.

Study Design

Blood was drawn to determine LH, FSH, testosterone, and creatinine levels in all patients. Inhibin B was determined in six patients. Semen samples were collected for semen analysis in five patients. Tanner stage and testicular volume were determined in all patients using the Prader orchidometer. A testicular ultrasound was performed in two patients. A testicular biopsy was performed in one patient with unwanted childlessness 10 years ago. Spermatogenesis in the biopsy was evaluated using the Johnson score (assessment of the quality of spermatogenesis based on number and furthest maturation stage present, with a score of "10" being optimal with normal numbers of spermatozoa present, and a score of "1" representing total absence of germ cells and Sertoli cells) (8). Glomerular filtration rate (GFR) was calculated as creatinine clearance by the Cockroft–Gault formula: C creat = (140-age) × weight/serum creatinine (9). The results were corrected for body surface area. Information on these data from previous years was obtained from the patients' medical records. The mean cystine level in polymorphonuclear leukocytes was calculated from data collected over the past 7 years. Before that time, cystine levels were determined using mixed leucocytes, which has proven to be less accurate (10). Therefore, these data were not used in the current study.

RESULTS

Median cystine levels in polymorphonuclear leukocytes was 0.6 (range = 0.3–1.5, heterozygote level <0.5) nmol/mg protein. The dose of cysteamine was evaluated two to four times yearly, and was increased when cystine values were above the heterozygote range. Median cysteamine dose at the time of the study was 2,400 (range = 1,200–4,200) mg per day, divided in three or four doses (Table 1).

Median testis volume was 18 (range = 10–18) mL. Patient 1 had a Tanner stage P3G3, patient 2 had Tanner stage P5G5, the other five patients had Tanner stage P4G4. The median GFR was 60 (range = 10–110, normal >90) mL/min/1.73 m^2; the median LH and FSH levels were 12.3 (range = 7.4–235.0, normal 1.4–8.5) E/L and 28.7 (range = 6.8–298.0, normal 1.5–11.0) E/L, respectively. The median plasma testosterone level was 16.1 (range = 8.7–31.3, normal 11.0–45.0) nmol/L. Median plasma inhibin B level was 78 (range = 10–210, normal = 150–400) ng/L (Table 1). Hormonal status was completely normal in patients 2 and 5.

All of the collected sperm samples showed azoospermia, with a normal volume (except for patient 3) and pH (Table 1). The testicular ultrasounds in two patients showed mild interstitial fibrosis. The testicular biopsy in one subject (patient 4) performed at the age of 33 years showed a Johnson score of 8 to 9, indicating sufficient spermatogenesis and total development in most seminiferous tubules (Fig. 1).

DISCUSSION

As far as we know, this is the first study of the fertility status of male cystinosis patients under cysteamine treatment. Although testicular function is known to depend on renal function (7), in male cystinosis patients not treated with cysteamine the dysfunction of the pituitary–testicular axis seems to be related to the metabolic disease and not only to a degree of renal failure (6). In our study of seven male cystinotic patients treated with cysteamine, only two (patients 2 and 5) had a normal sex hormone status and a normal GFR. Interestingly, patient 6 who had a low GFR of 15 mL/min/1.73 m^2 had only moderate increased LH and FSH levels (12.3 and 28.7 E/L, respectively), whereas patient 7, who had the highest LH and FSH levels (115.4 and 264.0 E/L, respectively) had a GFR of 100 mL/min/1.73 m^2. This suggests that renal function is not the dominant factor disturbing the testicular function of male cystinosis patients.

The most striking finding in our study is that all of the analyzed semen samples showed azoospermia, even in patients with a normal hormonal status. The origin of the azoospermia remains unclear. Testicular ultrasound showed only mild interstitial fibrosis and no signs of obstruction. Whether cysteamine can penetrate the blood–testes barrier and deplete testicular cystine accumulation is not known so far.

Treatment with cysteamine itself may play a negative role on fertility in male cystinosis patients. Cysteamine is known to decrease plasma somatostatin levels, which in turn, can inhibit ghrelin release, a protein produced in the stomach and gut (11). In rats, cysteamine administration results in an increase of ghrelin plasma levels (12). Ghrelin diminishes testosterone production and spermatogenesis by its negative effect on both Sertoli and Leydig cells (13). Whether spermatogenesis in cystinosis patients is inhibited by the use of cysteamine should be further investigated.

Chik et al. described germinal dysplasia, increased fibrosis, and Leydig cell hyperplasia in the histologic examination of the testicular tissue of a cystinosis patient who died of an aspiration pneumonia. He was not treated with cysteamine. The testicular biopsy performed in our patient 4, who was treated with cysteamine starting from the age of 18 years and having cystine levels always within the heterozygote level, showed a marked fibrosis with no germinal dysplasia and no signs of inflammation. The Johnson score was 8 to 9,