Follow-up and treatment of adults with cystinosis in the Netherlands

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Abstract

Background. Cystinosis is a rare autosomal recessive disease, caused by intracellular cystine accumulation due to a defect in the lysosomal cystine carrier. Treatment with cysteamine favours the transport of cystine out of the lysosomes, diminishes organ damage, and postpones the progression of renal failure. The extra-renal deposition of cystine continues after renal transplantation, leading to later complications. The objective of this study was to evaluate the follow-up, the occurrence of late complications, the social status, and the adequacy of cysteamine treatment in adult patients with cystinosis.

Methods. The medical histories of 10 adult cystinosis patients aged 19–36 years were studied. The impairment of thyroid function, central nervous system, endocrine pancreas, and ocular manifestations, as well as treatment with cysteamine were evaluated.

Results. Eight patients received in total 12 renal grafts, one patient was dialysed and one received conservative treatment for chronic renal failure. Extra-renal complications were noted in six patients, loss of visual acuity in four, hypothyroidism in three, diabetes mellitus in one, cerebral atrophy and epilepsy in one, and swallowing difficulties in two patients. Ophthalmic control was not performed in two patients, thyroid function was not controlled in two and glycaemia not controlled in two patients. Seven patients received 2100–4000 mg cysteamine per day in 2 (n = 2), 3 (n = 1), 4 (n = 3), or 6 (n = 1) doses. Cystine concentration in leukocytes was measured once or twice a year in eight patients and was within the recommended range only in three patients.

Conclusion. A high rate of extra-renal complications in adults with nephropathic cystinosis was found. Optimizing the cysteamine therapy may attenuate these complications. Better communication between paediatric and ‘adult’s’ nephrologists is needed to improve follow-up and treatment of grown-up cystinosis patients.

Keywords: adults; autosomal recessive; cysteamine treatment; cystinosis; extra-renal involvement

Introduction

Cystinosis, a rare autosomal recessive disease, caused by intracellular cystine accumulation due to a defect in the lysosomal cystine carrier, occurs in approximately 1 in 100,000–200,000 live births [1]. The cystinosis gene, CTNS, identified by positional cloning strategy, has been mapped to the short arm of chromosome 17. This gene encodes a protein, named cystinosin, with features of a lysosomal membrane protein [2].

Renal Fanconi syndrome, an early clinical manifestation of the infantile form of nephropathic cystinosis, generally becomes apparent 3–6 months after birth. Untreated patients usually develop end-stage renal disease (ESRD) before the age of 10 years, with a wide range up to 20 years [3]. Late-onset form of cystinosis generally appears at the age of 12–14 years, often does not presents with complete Fanconi syndrome, but may progress to ESRD within a few years of diagnosis [1]. An aminothiol, cysteamine, depletes intralysosomal cystine content by reacting with cystine to form cysteine–cysteamine mixed disulphide and cysteine, which can leave lysosomes via lysosomal lysine and cysteine carriers respectively. However, cysteamine does not reverse Fanconi syndrome and only postpones the commencement of renal-replacement therapy. After renal transplantation, the ongoing accumulation of cystine causes multi-organ damage: photophobia and loss of visual acuity due to corneal cystine crystals and retinopathy, bradykinesia, dementia, convulsions or spasticity due to cerebral atrophy, basal ganglia and periventricular calcifications or ischaemic lesions, muscle weakness and swallowing difficulties due to vacuolar myopathy, hypothyroidism, exocrine pancreas deficiency and diabetes mellitus [4–9]. Growth retardation, delayed puberty, hypogonadism and male infertility are frequent [10,11]. These serious late complications require the continuation of cysteamine treatment after renal transplantation in order to diminish extra-renal cystine...
accumulation [12]. Regular measurement of intracellular cystine is indicated to control the efficacy of cysteamine treatment in pre- and post-transplant patients [13].

The aim of the study was to evaluate the follow-up, the occurrence of extra-renal complications, the social status, and the adequacy of cysteamine treatment in adult patients with nephropathic cystinosis in the Netherlands.

Subjects and methods

A retrospective analysis of case histories of 10 adult cystinosis patients who were followed in five Netherlands university hospitals was performed. The diagnosis of cystinosis was based on the evidence of cystine corneal crystals or elevated leukocyte cystine level. The impairment of thyroid function, central nervous and muscular system, endocrine pancreas and ocular manifestations, the social status of the patients, and treatment with cysteamine (dose, frequency, and cystine measurements in leukocytes) were evaluated. Cystine leukocyte content was measured by HPLC in the same laboratory [14].

Results

Characteristics of the patients

The patient’s age range was 19–36 years, there were six male and four female patients. Cystinosis was diagnosed during the first decade of life in all patients. At presentation, all patients had renal Fanconi syndrome and cystine corneal crystals. The median age at diagnosis was 3 years.

Renal replacement therapy (RRT) was initiated at median age of 12 years. Eight patients received in total 12 renal grafts, one patient dialysed and one had chronic renal failure and received conservative treatment. Among the transplanted patients, six had well functioning renal grafts and two had pre-terminal graft failure due to chronic rejection (Table 1). Renal graft loss was not related to the cystinosis and was caused by arterial bleeding after the graft biopsy in patient no. 2, acute rejection (first graft), renal-artery stenosis and chronic rejection (second graft) in patient no. 5, and membranous glomerulopathy and chronic rejection in patient no. 10.

Extra-renal organ involvement (Table 1)

No patient died. Six patients suffered from major extra-renal complications. Two patients had multiple extra-renal organ involvement.

Visual acuity. Four patients had loss of visual acuity due to excessive cystine corneal accumulation, retinopathy at fundus examination in patients nos 1 and 5, and band keratopathy in patient 10. Two patients received no ophthalmic control.

Endocrine complications. One patient had insulin-dependent diabetes mellitus, three had hypothryoidism and required thyroid hormone treatment. The thyroid gland function was not controlled in two patients. The glycaemic control was not performed in three patients and only occasionally in three other patients. Gonadal function was not assessed in any patient.

Central nervous system and muscle involvement. Patient no. 8 had epilepsy with evidence of periventricular calcifications and cerebral atrophy on computer tomography of the brain. Two patients had swallowing difficulties due to myopathy. Patient no. 1 had mild dysphagia. In patient no. 10, swallowing problems appeared at the age of 22 years, predominantly during the passage of food through the pharynx, and were not progressive. At the age of 31 years he presented with complaints of dysphonia. The evaluation revealed no heart involvement, but
decreased force of respiratory muscles. Lung function examination showed a restrictive respiratory dysfunction. He was advised to stop smoking, which resulted in short reduction in complaints. Later, dyspnoea increased and was a cause of severe disability.

Growth

The median length of male patients was 164.50 cm (–3.70 SD) and of female patients 157.50 cm (–2.50 SD).

Social status, education, and integration

Three patients did not complete any professional study, two were still occupied with low and intermediate professional education, and five received low or intermediate education and were working (Table 1). Patients nos 8 and 10 have a stable relationship.

Cysteamine treatment (Table 2)

Median age at start of cysteamine therapy was 14 years (range 3–25). At the time of evaluation, seven patients were receiving oral cysteamine treatment. The dose varied from 40 to 70 mg/kg cysteamine base per day in 2 (n=2), 3 (n=1), 4 (n=3) or 6 (n=1) doses.

Three patients were not treated with cysteamine: one because of the patient’s refusal (no. 5), and two patients did not receive a prescription from their physicians. Patient 4 was obviously not compliant with the prescribed medication.

In two patients no measurements of cystine levels in the leukocytes were done. In eight patients cysteamine was measured at least once a year; at last measurement median cystine content was 0.35 with a range of 0.072–3.00 nmol/mg protein. Only three patients had leukocyte cystine content within the recommended range (<0.2 nmol/mg protein). No information about the interval between the last cysteamine dose and the time of blood examination was available.

Cysteamine eye drops were not administered in four patients.

Relation between cysteamine treatment of the occurrence of late complications

Among the three untreated patients, one (no. 5) had a severe course of the disease with multiple complications, including diabetes mellitus, epilepsy, and retinopathy. Patient no. 6 had impaired thyroid function, but patient no. 7 has not yet any extra-renal organ involvement.

Two patients treated according to the guidelines (nos 3 and 8) had no extra-renal complications.

Discussion

Renal transplantation and the availability of cysteamine treatment have transformed cystinosis from a fatal paediatric disease into a treatable one with which patients can survive into adulthood.

The evaluation of 36 adult American cystinosis patients, aged 17–34 years revealed a high rate of mortality and morbidity [15]. Seven patients died at ages between 18 and 34 years from aspiration, pseudobulbar palsy, uraemia, or unexplained sudden death. Twenty-two per-cent of the patients were blind or had severely impaired vision, 86% required thyroid hormone replacement, 30% had distal myopathy, and more than 60% had swallowing difficulties. Only 11 of 36 patients received an adequate cysteamine treatment [15].

Adult cystinosis patients are generally followed up by nephrologists, who pay major attention to the renal function, risks of renal osteodystrophy, hypertension, and other symptoms shared by all nephrological patients. The purpose of this study was to evaluate the adequacy of the follow-up and treatment of adult cystinosis patients, as they suffer from additional complications related to cystinosis and require specific cysteamine treatment.

Case histories of all Dutch adult cystinosis patients, followed in five University hospitals, were studied. Despite the fact that the diagnosis of cystinosis was made before the age of 10 years and all patients had

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<th>Patient no.</th>
<th>Age at start cysteamine (years)</th>
<th>Duration of cysteamine (years)</th>
<th>Daily cysteamine (mg/kg)</th>
<th>Cysteamine daily doses (times per day)</th>
<th>Cystine measurements (per year)</th>
<th>Last leukocyte cystine content (nmol/mg protein)</th>
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*not treated; **not measured.

Table 2. Cysteamine treatment of adult cystinosis patients
Fanconi syndrome at presentation, this series of patients was not homogenous. Patients 1, 6 and 10 reached ESRD at the age of 17–18 years, which is later than classically described in patients with an infantile form of cystinosis. Cysteamine treatment was not likely to explain the late onset of ESRD as it was either not administered or was administered late. Surprisingly, patients 1 and 2, who are siblings, developed terminal renal failure at the ages of 10 and 18 years respectively. The data from European Dialysis and Transplant Association Registry showed the median age at the start of renal replacement therapy to be 9.5 years, with a wide range of 1–20 years. No information on cysteamine therapy or clinical presentation was available in this database [16].

Patient no. 8 presented at the age of 9 years with Fanconi syndrome and cystine crystals in the cornea. Cysteamine was administered only at the age of 17 years. However, at the age of 30 he still did not receive renal replacement therapy, which prevents his being classified as having an infantile form of cystinosis. Attard et al. [17] also described two patients, presenting at early age with classical infantile cystinosis, who did not develop renal failure at the age of 18 and 22 years. DNA analysis showed that these patients had at least one mutation, presumably permitting the production of some functional protein, which could account for their milder phenotype [17]. We did not perform mutation analysis in our studied patients, but believe that the diversity of genotype could explain their different clinical courses.

The morbidity of Dutch cystinosis patients, with an exception of visual impairment, was lower than in the American series, possibly due to the amelioration of cystinosis treatment during the last decade. A milder course of the disease in some patients could be another explanation for this lower morbidity.

Seven of 10 Dutch adult patients were treated with cysteamine compared to 30% Americans; however, only three of 10 patients had the recommended leukocyte cystine level. Cystine was measured in the mixed leukocyte preparation by the HPLC method in the same biochemical laboratory, which excluded methodological differences in the determination. According to the laboratory guidelines, blood for cystine determination has to be taken before the next cysteamine dose. However, we were not able to determine whether this recommendation was always followed. Measured by the HPLC method, cystine value in healthy controls (n = 15) was 0.04–0.013 and in the obligate heterozygotes (n = 15) 0.03–0.2 nmol/mg protein. As the cystine leukocyte level necessary to prevent the progression of renal disease and the occurrence of extra-renal complications is unknown, the upper heterozygote value was recommended as an upper limit of cystine before the next dose of cysteamine is given. We have recently changed from measuring cystine in mixed leukocytes to the granulocyte preparations, as cystine preferentially accumulates in the granulocytes. Heterozygote value was significantly higher when measured in the granulocytes (0.11–0.63). However, as all previous measurements have been done in the mixed leukocyte preparations, we used the last cystine leukocyte value to evaluate the current status of the patients.

No uniform follow-up and treatment strategy was applied by Dutch nephrologists. While renal function and arterial hypertension were assessed at each ambulatory visit, the extra-renal organ involvement relating to cystinosis was evaluated only occasionally or not at all. Two nephrologists did not prescribe any cysteamine treatment. Even when the measured cystine leukocyte content was above the recommended level, the dosage of cysteamine was not systematically adapted. Three patients received cysteamine in 2–3 doses, which is insufficient as the leukocyte cystine content returns to its original levels as early as 4–6 h after the cysteamine dose [18].

Cysteamine eye drops are effective in reducing photophobia and density of corneal crystals in cystinosis patients; however, four patients did not receive this treatment. The effectiveness depends on the concentration and the number of daily instillations: a dose of 0.5% at 5–6 times a day is recommended [19].

We have no information on compliance with the cysteamine therapy, except in patient no. 4, who was obviously non-compliant. Non-compliance also could be suggested in patient no. 10, who had a high leukocyte cystine content despite adequate cysteamine prescription. Non-compliance with cysteamine treatment is a difficult problem, as for patients the potential later benefits of cysteamine do not always outweigh the more immediate inconveniences such as an unpleasant odour or gastrointestinal discomfort.

In summary, the finding of a high incidence of extra-renal complications in adult Netherlands cystinosis patients, and a rather unsystematic follow-up, indicate the necessity of optimizing the care of these patients. Better communication between paediatric and ‘adults’ nephrologists is required in order to continue adequate follow-up and treatment of cystinosis patients growing into adulthood. A minimum requirement would be an annual neurological examination, including the evaluation of the strength of oropharyngeal and hand muscles, and an ophthalmological examination, regular determination of plasma TSH, T3 and glycaemic control, as well as measurement of intracellular cystine content at least twice a year.

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References


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