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Infantile Nephropathic Cystinosis

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SUMMARY

Introduction Infantile nephropathic cystinosis (INC) is a metabolic disorder due to impaired carrier-mediated transport of cystine out of cellular lysosomes.

Objective To examine the prevalence and clinical characteristics of INC in paediatric patients with end-stage renal disease (ESRD) in Serbia and give a recent statement of the disease.

Methods ESRD database of the Centre for Paediatric Renal Replacement Therapy (RRT) in Serbia was used to identify all patients with INC who started RRT before age of 19 years during the period January 1980 – December 2008; their records concerning clinical characteristics, therapy and outcome were evaluated.

Results Only three of 298 paediatric patients with ESRD had INC. The first signs of the illness were recognised during infancy. Fancony syndrome was diagnosed in the second year, but the diagnosis of cystinosis was delayed at mean 6 years. ESRD occurred in the first decade of life. All patients underwent cadaver kidney transplantation. At the end of the study period all patients were alive. A 31-year-old female patient was on maintenance chemodialysis due to graft failure after functioning for 11 years. She was growth retarded, single, unemployed, with severe signs of renal dystrophy. Two male patients (14.3 and 14.7 years old) had normal graft function, normal education, and good quality of life, although they were also severe growth retarded.

Conclusion The prevalence of infantile nephropathic cystinosis is low in Serbia. The diagnosis of cystinosis was delayed in all patients, although they exhibited the typical course of the disease.

Keywords: end-stage renal disease in children; heritable nephropathy; Fancony syndrome

INTRODUCTION

Cystinosis is a rare autosomal recessive metabolic disorder due to impaired carrier-mediated transport of cystine out of cellular lysosomes. The cystinosis gene, CTNS, resides on chromosome 17p13 [1]. It has 12 exons (the first two of which are non-coding) and encodes an integral lysosomal membrane of the protein called cystinosin, which contains 367 amino acids and functions as a cystine carrier [2, 3]. More than 80 different genetic mutations of CTNS have been described of which the most common is a 57-kb deletion that has been reported either in homozygosity or heterozygosity in approximately 75% of patients from northern Europe, 35% of patients from northern America and 20% from southern Europe [4, 5]. The severity of the cystinosis correlates directly with the amount of cystine storage and indirectly with the amount of residual cystine transport capacity [6].

The most common and the most severe form of cystinosis is infantile nephropathic cystinosis (INC) which is found in 94-96% of cases, starting during infancy with progressive Fancony syndrome and later glomerular impairment leading to end-stage renal disease (ESRD) in the first decade of life. In late-onset (also called intermediate, juvenile, or adolescent) nephropathic cystinosis symptoms generally are not diagnosed before age 12 years and the disease progresses slowly over time. Adult (benign or non-nephropathic) cystinosis begins in adulthood and does not results in kidney impairment. Cystine crystals accumulate in the cornea and conjunctiva of the eye due to which photophobia is present. Individuals with infantile cystinosis carry 'severe' mutations on both alleles, whereas individuals with milder forms of the disease carry either one 'severe' and one 'mild' mutation, or two 'mild' mutations [6].

An estimated incidence of INC is about 1 in 100–200,000 live births. However, a higher incidence has been reported in some subpopulations [7]. In the 20-year period (1975–1994), 333 patients with INC were reported from 23 European and Mediterranean countries, as starting renal replacement therapy (RRT) before 20 years of age; the median age was between 9 and 10 years [8].

OBJECTIVE

INC in Serbia is underreported [9]. Therefore, the aim of our study was to examine the prevalence of INC in ESRD paediatric patients in Serbia and give a recent statement regarding clinical presentation, diagnosis, and treatment of this disease.

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METHODS

The ESRD database of the Centre for Paediatric RRT in Serbia was used to identify all patients with INC who started RRT before age of 19 years during the period January 1980 – December 2008; their records concerning renal involvement were retrospectively evaluated, while late extrarenal complications were prospectively investigated. Endocrinological, electromyographc and ophthalmic examinations were also performed.

RESULTS

Only three out of 298 paediatric patients with ESRD treated by RRT in Serbia from January 1980 until December 2008 had INC: one girl from central Serbia and two boys from southern Serbia. None of the patients reported parental consanguinity, although it was highly suspected in one patient from southern Serbia due to HLA matching and finding of maternal corneal cystine crystals. The clinical, renal and extrarenal manifestations of INC of our patients are presented in Tables 1, 2 and 3 and Figures 1 and 2.

The patients were asymptomatic at birth and developed normally until 6-10 months, when they manifested failure to thrive, vomiting, constipation, polyuria and excessive thirst, periods of dehydratation, poor growth and rickets. However, Fancony syndrome was recognised by the second year, while cystinosis was diagnosed at mean age of 6.3 years. ESRD occurred from 7 to 8 years of age. All patients underwent cadaver kidney transplantation after mean 2.5 (0.3-5) years of chronic haemodialysis. Besides supportive treatment, two male patients received thyroid substitution and cysteamine therapy which was rather irregular due to lack of supply. The oldest, female patient has never received cysteamine therapy.

At the end of the study period all patients were alive; female patient was aged 31 years. She restarted chronic maintenance haemodialysis at age 22 years, 11 years after being transplanted. Her graft failed due to its chronic dysfunction. She was growth retarded with severe signs of renal osteodistrophy (Figure 1). Unfortunately, she remained only elementary educated, single and unemployed.

At the end of follow-up, two male patients were 14.3 and 14.7 years old, with normal graft function. They were on regular education, but severely growth retarded (mean SDS of -3.3) and with a mild pubertal delay.

All patients had extended form of ocular cystinosis (Figure 2).

Table 1. Clinical characteristic of the patients

Parameter		Patient		
		1	2	3
Gender		Female	Male	Male
Ethnicity		Caucasian	Caucasian	Caucasian
Birth place		Central Serbia	South Serbia	South Serbia
Familial history		Not remarkable	Not remarkable	Mother: corneal cystin deposits
Consanguinity		Not known	Not known	Not known
Age at first symptoms (years)		0.5	0.9	0.9
Age at diagnosis (years)		4.8*	6.0**	6.0**
Age at the end of follow up (years)		31	14.7	14.3
Diagnosis based on:	Fancony syndrome	Yes	Yes	Yes
	Corneal cystin deposits	Yes	Yes	Yes
	White blood cells cystin	6.1 µmol/g protein	Not done	Not done
	Renal failure	Yes	Yes	Yes
	Kidney biopsy	Not done	Not done	Not done
	Genetic test	Not done	Not done	Not done
Therapy	Supportive	+ chronic haemodialysis	+ immunosuppressive	+ immunosuppresive
	Thyroid hormones	No	Yes	Yes
	Growth hormone	No	No	No
	Cisteamine	No	Yes, irregular	Yes, irregular

* Diagnosis was performed at the University Children's Hospital in Belgrade
** Diagnosis was performed at the Institute for Child and Mother Health in Belgrade

Table 2. Renal disease in patients with cystinosis

Patient	Age at diagnosis			RRT	Duration of RRT (years)	Renal function at the end of follow-up
	Fancony Sy (months)	Renal failure (years)	ESRD (years)			
1	13	3	7	CHD RT (Cad) CHD	4 11 9	ESRD
2	11	6	7	CHD RT (Cad)	2.7 5	Normal
3	16	6	8	CHD RT (Cad)	0.3 6	Normal

ESRD – end-stage renal disease; RRT – renal replacement therapy; CHD – chronic haemodialysis; RT – renal transplantation; Cad – cadaveric

Table 3. Extrarenal complications of cystinosis

Patient	Ophthalmic	Growth – SDS	Thyroid function	Diabetes mellitus	Gonadal function	CNS	Myopathy
1	Crystals deposited in the cornea, conjunctiva and iris, hypermetropia	Retarded – 30 cm below genetic target height	Normal	No	Normal	Normal	Yes
2	Crystals deposited in the cornea	Retarded – -3.1	Hypothyreosis	No	Delayed puberty	Normal	NT
3	Crystals deposited in the cornea	Retarded – 3.5	Hypothyreosis	No	Delayed puberty	Normal	NT

SDS – score of standard deviation for height; CNS – central nervous system; NT – not tested

Figure 1. Patient No 1: 31-year-old female

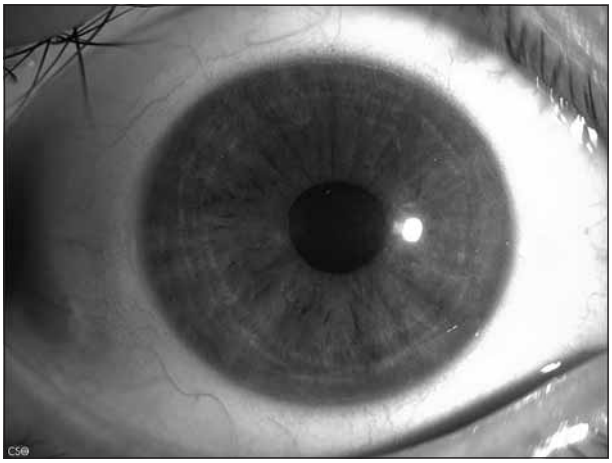

Figure 2. Slit lamp photography of the eye (patient 1) showing cystine crystals in the cornea and iris

DISCUSSION

From this epidemiological survey, it appears that INC is a very rare disease in Serbia. It may be underestimated during infancy due to its unspecific symptoms like those in severe gastrointestinal or endocrinological disorders. Urine volume can be so great that some of the patients are diagnosed with nephrogenic diabetes insipidus and pseudohypoaldosteronism [10]. Hypophosphatemic rickets, with high fractional excretion of phosphate, normal vitamin D levels, and elevated levels of serum alkaline phosphatase, is characterised by osteomalacia, bone deformities and delayed ambulation [10]. The hypercalciuric hypocalcemia of cystinosis can cause tetany. Fancony syndrome also causes tubular low molecular proteinuria, but in some predialysis patients urinary protein levels may be in nephrotic range.

At the beginning of the disease the diagnosis may be difficult, but the disorder is recognised as most common and most treatable identifiable cause of renal Fancony syndrome in children. Later on, one cannot miss the diagnosis of INC leading to ESRD during the first decade of life.

According to a well done Italian Registry of paediatric chronic renal failure INS accounts for approximately 3.4 % of terminal renal failure in children [11]. The European Dialysis and Transplant Association Registry found that the median age of children starting renal replacement therapy for cystinosis was 9.5 years [12]. Being autosomal recessive inborn error of metabolism it is more common in regions where consanguinity marriage rate is high, such as found in Iran [13]. On the contrary, countries with a low rate of consanguinity, such as Nordic countries have the lowest incidence and prevalence of INC [14]. The low incidence of consanguinity in Serbia may also contribute to the low incidence of INC.

The clinical course of INC in our patients was very typical. Nevertheless, the diagnosis was delayed in all of them. It was based mainly on clinical findings of Fancony syndrome, renal failure and corneal cystine crystals, except in the first patient in whom it was also confirmed biochemically by finding of increased concentration of cystine in leukocytes. This test was performed elsewhere, and still now it is not done in our country. White blood cells prove an easy accessible tissue, and are therefore useful in the measurement of cystine levels. Normal individuals have a cystine level of less than 0.2 nmol ½ cystine/mg protein, while homozygous patients with INC have more than 10 time higher concentrations of cystine.

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Cystinosis was first thought to be a purely renal disease; however, with the advent of renal replacement therapy it was found to lead to widespread organ damage. This includes ocular, endocrinological, hepatic, muscular and central nervous system complications [10]. Extrarenal cystine accumulation may be prevented or at least delayed by using regularly the drug cysteamine, which cleaves cystine molecules, thereby allowing their clearance from the lysosome. Unfortunately, none of our patients received regularly cysteamine therapy due to the lack of its supply in Serbia. Moreover, the oldest female patient has never received this drug. Therefore she manifested late complications of cystinosis including growth failure, osteomuscular, and ophthalmic complications.

Growth retardation is almost obvious clinical complication of cystinosis, being much worse than in children with ESRD due to other causes [15]. Acidosis, metabolic bone disease, hypophosphatemic rickets, nutrition losses and hypothyroidism contribute to profound growth retardation in children with cystinosis. Treatment with growth hormone significantly improves height velocity in prepubertal cystinosis patients [16]. All our patients had growth retardation. Adult height of the first patient was 30 cm below that estimated according to her parents' height, and the other two patients were also severely growth retarded with mean SDS of -3.3.

Hypothyroidism occurs frequently in patients with cystinosis due to extensive destruction and infiltration of the epithelium of thyroid glands with cystine crystals and pituitary resistance to the thyroid hormone [10]. Treatment by thyroxine returns to normal functional consequence of hypothyroidism. Our male patients have been receiving thyroxin due to hypothyroidism while female patients had normal function of thyroid gland. Same was with gonadal function. The male patients exhibited delay in sexual maturation, but the female patient had normal gonadal endocrine parameters. Hypergonadotropic hypogonadism is a well known cause of delayed puberty (starts at 16-17 years of age) in male cystinotic patients who are also infertile [16]. Impairment of glucose tolerance and diabetes mellitus are late complications of cystinotic process which gradually alters β cell function over the years. Therefore, more than half of the patients become insulin-dependent by the age of 25 years [17].

Ocular manifestation includes crystallisation of cystine in the cornea and conjunctiva, pigmented retinopathy, focal destruction of photoreceptors and devascularisation. Corneal crystals usually appear as needle-shaped reflective opacities visible on a slit lamp, progressing from the peripheral to central surface. These crystals can be observed very early in life, as soon as age three months, and is almost constant after age one year, being therefore pathogonomic ocular finding for the diagnosis of cystinosis. In INC, whole cornea is generally involved after age seven years. Retinopathy can be observed as soon as 3 years, and is almost constant after 7 years [18]. Stromal oedema is responsible for photophobia, whereas epithelial ulcerations provoke an exposition of underlying corneal nerves with pain, watering and blepharospasms. Cysteamine eye drops up to 12 times a day are effective to reduce photophobia and density of corneal crystals [19]. All of our patients had ocular involvement, but they did not use cysteamine eye drops due to the lack in supply.

Bone involvement manifested bone fragility due to osteopenia and crystals deposition, while muscular atrophy resulted in decreased strength of trapezius and shoulder muscles. Electromyography done in patient 1 documented cystinotic myopathy of both hands, both arms and lower extremities.

Cystinosis encephalopathy is a late complication of INC that could be the consequence of cystine crystals accumulated especially in basal ganglia, in cerebral arterial walls, but also in cerebral perycites due to alteration in blood brain barrier [20]. All of our patients had normal mental status.

Gastrointestinal complications are late and include swallowing difficulties attributed to accumulation of cystine in oropharyngeal muscles [10]. Hepatosplenomegaly, sometimes with hypersplenism, as well as pancreatic exocrine insufficiency have been also reported as late extrarenal complications. We did not find gastrointestinal complications in our patients. On the other hand cysteamine may cause gastrointestinal discomfort, perhaps due to stimulation of gastric acid and gastrin production [21].

Treatment of INS should involve a team approach, including a paediatric nephrologist, metabolic disease expert, genetic counsellor, ophthalmologist, endocrinologist and a dietician [22]. Principle therapeutic issues include: a) ready access to water (2-6 l per day), sodium (2-6 mmol/kg/day), potassium (2-6 mmol/kg/day), bicarbonate (2-15 mmol/kg/day) and phosphate, b) Vitamin D (alphacalcidol or calcitrol at 0.2-1 μg/day), c) oral cysteamine gradually increasing to achieve the dose of 60 mg/day and cysteamine eye drops up to 12 times per day , as well as other supportive treatment depending on kidney impairment and extrarenal complications. Oral cisteamine therapy provides the mainstay of INC treatment and should be started as soon as possible. Prenatal diagnosis is available biochemically, based upon elevated cystine levels in both chorionic villi obtained at about 10^{th}–12^{th} gestational week by chorionic villus sampling and amniocytes obtained by amniocentesis usually performed at about 15^{th}–18^{th} gestational week [22].

CONCLUSION

The prevalence of ESRD due to INC is very low in Serbia. Early diagnosis is critical and relies upon the finding of failure to thrive and renal tubular Fancony syndrome. The diagnosis of cystinosis was delayed in all our patients, although they exhibited the typical course of INC. The main extrarenal complication of the disease included ocular crystals deposits, growth retardation, hypothyroidism, and musculoskeletal weakness. Oral cisteamine therapy provides the mainstay of INC treatment and should be started as soon as possible. This therapy was irregular in our patients due to difficulty in the supply of this drug

in Serbia. In order to improve the diagnosis and the treatment of INC in Serbia we have given a recent statement regarding clinical presentation, diagnosis, and treatment of this severe disease.

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Инфантилна нефропатска цистиноза

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КРАТАК САДРЖАЈ

Увод Инфантилна нефропатска цистиноза (ИНЦ) је наследна метаболичка болест која је последица нагомилавања цистина у лизозомима ћелија.

Циљ рада Циљ рада био је да се утврде преваленција и клиничке одлике ИНЦ код деце с терминалном инсуфицијенцијом бубрега (ТИБ) и сумирају савремена сазнања о ИНЦ.

Методе рада Урађена је ретроспективна анализа узрока ТИБ код деце која су лечена заменом функције бубрега у периоду 1980–2008. године. Издвојени су болесници који су имали примарну болест ИНЦ и за њих су анализирани клиничке одлике ИНЦ, терапија замене функције бубрега и исход лечења.

Резултати Од укупно 298 деце са ТИБ, код само троје је дијагностикована ИНЦ. Први знаци болести препознати су у периоду одојчета, Фанконијев синдром је дијагностикован у другој години, а дијагноза цистинозе постављена је у просеку у шестој години. ТИБ се развила у првој деценији живота. Свим болесницима је урађена кадаверична трансплантација бубрега. Примена цистеамина је била нередовна због тешкоћа у набавци овог лека у Србији. На крају периода клиничког праћења сви болесници су били живи. Болесница (31 година) се вратила на хроничну хемодијализу пошто је после 11 година трансплантирани бубрег престао да обавља своју функцију. Она је ниског раста, неудата, незапослена и има знаке тешке остеодистрофије бубрега. Код дечака (14,3 и 14,7 година) функција трансплантираног бубрега је нормална, они имају добар квалитет живота, али веома заостају у расту у односу на своје вршњаке.

Закључак Преваленција ИНЦ у Србији је ниска. Са постављањем дијагнозе овог обољења се каснило код наших болесника, мада се код њих испољио типичан ток болести.

Кључне речи: терминална инсуфицијенција бубрега; деца; наследна нефропатија; Фанконијев синдром

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