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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Jeune syndrome with renal failure

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SUMMARY

Introduction/Objective Jeune syndrome (JS) is a rare hereditary ciliopathy characterized by asphyxiating thoracic dystrophy, shortened limbs and brachydactyly. Extraskeletal anomalies such as chronic renal failure (CRF), hepatic fibrosis, and retinitis pigmentosa may be a part of the JATD phenotype.
The aim of this study is to present long-term follow-up of JS patients with early progressive kidney disease.

Methods This is a retrospective study of pediatric patients with JS and CRF who were treated at the University Children's Hospital between January 1980 and December 2014. The patients' data were retrospectively reviewed from the medical records.

Results There were thirteen patients from 11 families, five girls and eight boys mean aged 4.3 years at the time of diagnosis. All of the patients had characteristic skeletal findings, retinal degeneration and an early onset of CRF at age range from 1.5 to 7 years. Five patients had neonatal respiratory distress and congenital liver fibrosis was diagnosed in five patients. One patient died due to complications of CRF, while others survived during follow-up of mean 11 years. *IFT140* mutations were found in four genetically tested patients.

Conclusion The average incidence rate of JS with renal phenotype in Serbia was about 0.2 per one million of child population. Long-term survival of JS patients depends on renal replacement therapy, while skeletal dysplasia, growth failure, respiratory and eyes problems have impact on the patients' quality of life.

Keywords: asphyxiating thoracic dystrophy; osteochondrodysplasia; ciliopathies; neonatal respiratory insufficiency; terminal renal failure

INTRODUCTION

Jeune syndrome or asphyxiating thoracic dystrophy (JATD) belongs to a group of osteochondrodysplasia. It was first described in 1955 by Jeune et al. [1]. In 1992, the International Working Group on Constitutional Diseases of Bone classified Jeune syndrome as one of six short-rib dysplasia syndromes with or without polydactyly into Type I (Saldino–Noonan), Type II (Majewski), Type III (Verma–Naumoff), Type IV (Beemer–Langer), Jeune, and Ellis – van Creveld [2]. They all show a recessive mode of inheritance, frequently caused by mutations in primary cilia intraflagellar transport (IFT) genes [3, 4]. Primary cilia are non-motile hair-like sensory organelles on the surface of most cells of mammals, birds, amphibians, and fish. They have a structure of nine doublet microtubules emerging from a basal body that contains a pair of centrioles [5]. A microtubule- and ATP-dependent IFT governs bidirectional (anterograde and retrograde) cargo transport and delivery processes that are essential for primary cilia growth and maintenance and governs a variety of important cell signaling events that are key to normal human development [5, 6].

The main recognizable clinical feature of JATD visible immediately after birth is a small, narrow chest and variable limb shortness, while extra skeletal organ involvement may occur later in life [7]. Fatal, early neonatal respiratory insufficiency may occur. Respiratory problems may be difficult to manage, but bilateral thoracic expansion offers an effective reduction in ventilator requirements in children with severe condition [8].

Approximately, one third of JATD patients display a nephronophthisis-like nephropathy with progression to terminal renal failure. There isn't enough data in literature concerning their long-term follow-up.

The aim of this study is to describe thirteen JATD patients with renal phenotype who were followed up mean 11.2 years (range of 1–26 years).

METHODS

This is a retrospective study of pediatric patients with JATD who were treated at Departments of Nephrology and at Center for dialysis and transplantation of University Children's Hospital between January 1980 and December 2014. The patients' demographic data, clinical characteristics at presentation, laboratory data and radiographic findings, treatments, and

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outcomes were recorded through retrospective review of their medical records. Early course of the disease for four patients was previously reported [9].

RESULTS

We evaluated 13 patients from 11 families, five girls and eight boys. Their clinical characteristics are presented in Table 1 and Table 2. Five patients were familial cases; two sisters and two brothers, and one patient was a cousin of two affected brothers. The others were single cases in the family. Ages at the time of diagnosis of JATD ranged from 1.5 to 8 years, mean age was 4.3 years. In all patients, the diagnosis was made by pediatric nephrologists when the patients presented with chronic preterminal renal failure.

All of the patients had characteristic skeletal findings including a narrow bell-shaped chest with short and horizontal ribs that variably reduced the diameter of the thoracic cage, short limbs and brachydactyly, while only one patient had polydactyly. The patients shared similar radiological features, including irregular costochondral junctions, elevated clavicles, short iliac bones with a trident-shaped acetabular roof of the pelvis, short and wide long bones of the extremities, and cone-shaped epiphyses of phalanges of hands and feet (Figures 1–4).

Five patients had neonatal respiratory distress but only two of them remained prone to respiratory problems later in the disease course. All except one patient were growth retarded (height below the third percentile). In addition, all patients had retinal degeneration and chronic renal failure, and five patients had congenital liver fibrosis.

Genetic analysis was performed in four patients. *IFT140* mutations were found in all of them [10].

Only one patient died due to heart failure in pre terminal renal failure, while others survived during mean 11 years of follow-up. Renal replacement therapy was predominant for patients' survival, while skeletal dysplasia, growth failure, respiratory and eye problems had impact on the patients' quality of life. All the patients had normal psychosocial development. The three oldest patients had university education, normal jobs and normal, independent social life.

DISCUSSION

JATD is a rare autosomal recessive disorder with a variable prevalence estimated at one per 70,000–150,000 live births [4, 8]. It has been described that about 30% of JATD patients will have renal involvement [8]. During the study period, only 13 patients with JATD and renal involvement were identified at the Dialysis and Transplantation Center of the University Children's Hospital in Belgrade, which serve all pediatric patients with terminal renal failure in Serbia. Thus, the average incidence rate of JATD with renal insufficiency in Serbia was 0.4 per year or approximately 0.2 per one million of child population.

The diagnosis of JATD is based on clinical and radiological findings. A key factor in the early diagnosis of JATD is skeletal dysplasia manifested as abnormal small thorax causing a reduced thoracic capacity, short limbs and brachydactyly, with occasional postaxial or axial polydactyly of the hands [8]. All of our patients had thoracic and limb abnormalities, but only one patient was found to have polydactyly.

Early postnatal survival of patients with JATD is often dictated by respiratory insufficiency due to the restrictive chest cage. From the literature data the survival rates in infancy are 40–80% [7, 8]. Treatment is usually palliative respiratory support, while in severe cases bilateral thoracic reconstructive surgery offers satisfying functional and esthetic results [7, 8]. Respiratory problems tend to become less pronounced with age due to improved mechanical properties of the chest wall with growth. However, majority of the patients maintained a restrictive lung function

Table 1. Clinicalof characteristics of patients with Jeune syndrome (JATD)

JATD patients	1	2	3	4	5	6	7	8	9	10	11	12	13
Sex	M	M	F	M	M	M	M	M	M	F	F	F	F
Age at presentation (years)	8.5	3	3	4.5	6	6	2.5	5	1.5	3.5	7	3	6
Follow-up (years)	8	2	26	13	13.5	14	4.7	3	1	5	21	14	21
Genetic analysis*	–	–	–	*IFT140*	*IFT140*	*IFT140*	–	–	–	–	–	–	*IFT140*
NRI	+	+	–	+	–	–	–	+	–	+	–	–	–
Small thorax	+	+	+	+	+	+	+	+	+	+	+	+	+
Brachydactilia	+	+	+	+	+	+	+	+	+	+	+	+	+
Polydactylia	–	–	+	–	–	–	–	–	–	–	–	–	–
Cone-shaped epiphyses	+	+	+	+	+	+	+	+	+	+	+	+	+
Shortened legs	+	+	+	+	+	+	+	+	+	+	+	+	+
Short stature	+	+	+	+	+	–	+	+	+	+	+	+	+
Facial dysmorphism	+	+	+	+	+	+	+	+	+	+	+	+	+
Impairment of vision	+	+	+	+	+	+	+	+	+	+	+	+	+
Congenital hepatic fibrosis	+	+	+	–	+	–	–	–	–	+	–	–	–

JATD – Jeune asphyxiating thoracic dystrophy; M – male; F – female; NRI – neonatal respiratory insufficiency; * Genetic analysis in England [11]

Table 2. Symptoms and signs of renal disease

JATD patients	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years) when first symtoms were recognised	7	2.5	2	2	2.5	4	2	3	1.5	2	2	2	3
Polyuria	+	+	+	+	+	+	+	+	+	+	+	+	+
Polydipsia	+	+	+	+	+	+	+	+	+	+	+	+	+
Enuresis	+	–	–	+	–	+	+	–	–	–	–	+	–
Renal ultrasound showing reduced size of kidneys, unclear CM differentiation	Yes	Yes	Yes + Cysts at the CM junction	Yes + Cysts at the CM junction	Yes + Cysts at the CM junction	Yes + Cysts at the CM junction	Yes + Cysts at the CM junction	Yes + Cysts at the CM junction	Yes + Cysts at the CM junction	Yes	Yes + Cysts at the CM junction	Yes	Yes
CRF, age (years)	8.5	3	3	4.5	6	6	2.5	5	1	3	6	3	6
TRF, age (years)	9	4	5	4.5	6	6	2.8	5	–	5.9	10	6	6
Peritoneal dialysis	-	-	-	–	–	–	–	+	–	–	–	+	–
Hemodialysis	+	+	+	+	+	–	+	–	–	+	+	–	+
Kidney transplantation age (years)	–	–	10	5	9.5	7	3.5	7	–	6	10	11.5	9
Follow-up after transplantation (years)	–	–	15	11.5	12.5	6	3	0.1	_	1.5	12	4.5	17
Family renal history	–	–	–	Mother:renal cyst	–	Mother:scarred right kidney	Cousen with JATD 8 and 9; Mother: renal cyst	JATD 8 and 9 are brothers and their cousen is JATD 7	JATD 8 and 9 are brothers and their cousen is JATD 7	–	JATD 11 and 12 are sisters	JATD 11 and 12 are sisters	–
Outcome	Lost to follow-up	Lost to follow-up	Short stature, severe vision impairment, finished faculty	Short stature, eyeglasses for vision correction	Short stature, severe obesity	Eyeglasses for vision correction	Eyeglasses for vision correction	Short stature, eyeglasses for vision correction	Died at the age of 1.5 years	Short stature, eyeglasses for vision correction	Short stature, eyeglasses for vision correction, finished faculty	Short stature, eyeglasses for vision correction	Short stature, eyeglasses for vision correction, finished faculty
GFR (ml/min/1.73 m^2)	/	/	90	88	82	122	102	72	–	71	85	94	90

JATD – Jeune asphyxiating thoracic dystrophy; M – male; CRF – chronic renal failure; TRF – terminal renal failure; CM – corticomedullary; GFR – glomerular filtration rate

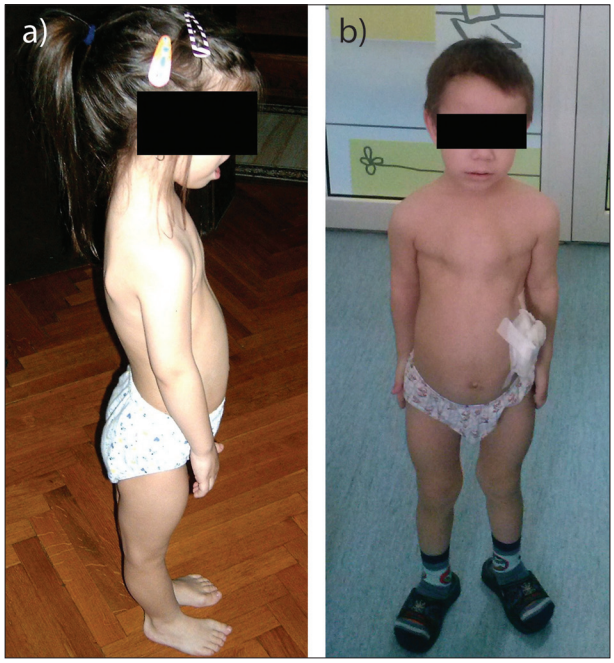

Figure 1. Clinical features of Jeune syndrome patients; a–b) Phenotypes of patients JATD 8 and JATD12 at five years of age; note disproportionate short stature with short extremities, relatively narrow thoraces with a protruding abdomen

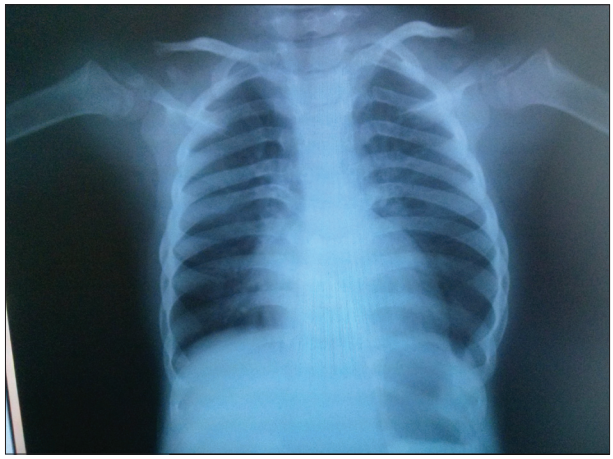

Figure 2. Thoracic features of Jeune syndrome: chest X-ray taken at the age of five years in patient JATD 8; note the narrow thorax, short ribs and elevated clavicles

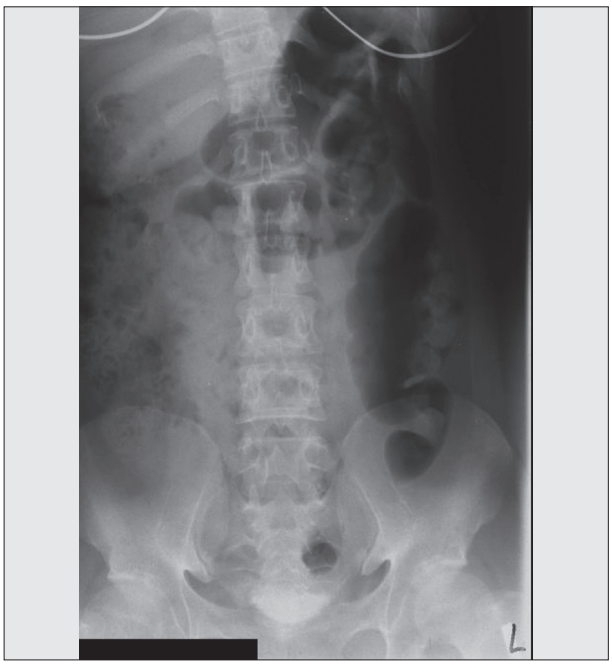

Figure 3. Characteristics of the pelvis of Jeune syndrome: X-ray of the pelvis of patient JATD 12 at the age of 20 years; note the typical trident appearance of the acetabula

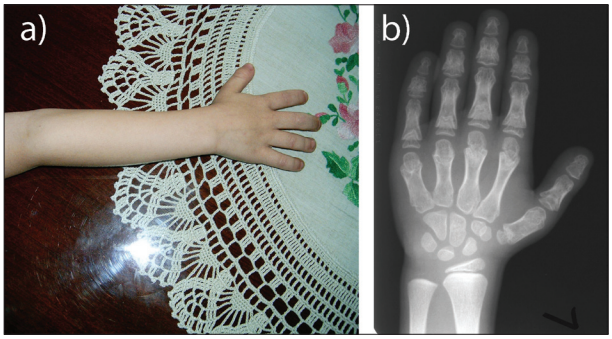

Figure 4. Brachydactyly in Jeune syndrome: a) typical broad hand with short fingers of the patient JATD 8; b) X-ray of the left hand of the same patient; note short and dysplastic phalanges

impairment resulting from lung hypoplasia. In our series, only five patients (38.5%) experienced respiratory problems in the infancy, and none died because of these. Two patients were prone to respiratory tract infection during further follow-up.

In contrast to milder respiratory problems in our patients, compared with those described in most articles [7, 8, 10–13], extraskeletal features affecting the eyes and kidneys were highly expressed later in life.

Retinal abnormalities are reported in 15–50%, but it may represent under-ascertainment [14, 15, 16]. All of our patients had documented retinal pigmented dystrophy by fundoscopy and/or electroretinography, but only half of them suffered of night blindness, usually manifested after the age of two years. Defective rhodopsin transport via the connecting cilium in retinal photoreceptor cells is proposed as the basis for the development of retinal dystrophy [16]. The ophthalmologic problems may cause gait instability which may prone them to trauma. That happened to one of our patients (patient No. 10), who had head trauma with subarachnoid hemorrhage and consecutive operative treatment at the age of 3.5 years. Five patients needed ophthalmologic correction by glasses due to hypermetropia.

Renal involvement has been reported in 17–20% of JATD patients [10–14, 17–20]. The kidneys are usually of normal or reduced size. The histological findings on renal biopsy include atrophic and cystic dilatation of the tubules, diffuse interstitial fibrosis, periglomerular fibrosis, and glomerular sclerosis. Cysts may develop typically at the corticomedullary junction [17]. Usually, clinical renal problems do not manifest until the second year of life and renal failure manifests at a median age of 13 years. Our patients had early onset of renal failure occurring at age range from 1.5 to seven years. Initial symptoms were relatively mild, started at approximately age of two years, and consisted of polyuria, polydipsia, and enuresis. That may be the explana-

tion of delayed diagnosis until the advanced stage of renal failure. No effective prophylaxis or treatment is available for renal involvement in JATD other than supportive care once chronic renal failure develops and dialysis and transplantation for terminal renal failure prove ineffective. One of our patients died at the age of 1.5 years due to cardiovascular complications of chronic renal failure. Other patients were on renal replacement therapy. Ten patients were successfully transplanted. As found by other authors [19], no recurrence of JATD was noted after transplantation.

JATD can be associated with periductal liver fibrosis, due to which patients develop hepatomegaly and moderate portal fibrosis with mild bile duct proliferation [8, 21]. Bile duct involvement in these cystic kidney diseases may be explained by the ciliary theory because the epithelial cells lining bile ducts (cholangiocytes) possess primary cilia. Five of our patients had mild liver affection.

The association of pancreatic fibrosis with Jeune syndrome has been described, but it has not been appreciated as a stable and important manifestation of this disorder [22]. None of our patients had pancreatic involvement.

Most of our patients exhibited short stature that can be explained by skeletal dysplasia and renal failure. Two patients had obesity that was difficult to treat with dietary measures. All patients had normal psychosocial development, doing well in school.

A lot of research has been done concerning a genetic diagnosis of JATD. A locus for JATD was mapped to chromosome *15q13* [23]. Work in animal models such as knockout mice suggests that defective IFT leads to impaired hedgehog signaling, which disturbs chondrogenic and osteogenic cellular proliferation and differentiation, leading to chondrodysplasia phenotypes [24, 25, 26].

Recently, five genes causing JATD have been reported, all encoding proteins involved in IFT (*DYNC2H1*, *IFT80/WDR56*, *IFT139/TTC21B*, *IFT144/WDR19*, *IFT140*) [4, 10, 15, 27–33]. *DYNC2H1* is a major gene responsible for JATD [27, 28, 29]. Phenotype–genotype correlations were recognized [27]. *IFT140* mutations in JATD seem to be causal only for a specific subset of cases with severe renal and prominent retinal involvement, in the context of heterozygous mutations potentially modifying the skeletal phenotype [10]. These mutations were documented in four of our patients, who were the only ones in whom genetic testing was done [10]. Having in mind that clinical features of the remaining patients, such as a non-lethal thorax-related clinical course, no polydactyly, retinal dystrophy, and an early onset of severe renal failure, were similar to those with documented *IFT140*, we can speculate that they also share the same genotype.

It is important to establish a correct diagnosis since JATD might recur within the family [8, 13, 33]. In our series of JATD patients, there were two sisters and two brothers. A prenatal sonographic diagnosis of Jeune syndrome at as early as 14 weeks of gestation in a fetus at risk for this condition has been reported [34]. Key factors in the prenatal diagnosis are the features of the skeletal dysplasia, polyhydramnios, and unidentifiable fetal respiratory movements [34, 35, 36].

Our survey demonstrates very encouraging results for long-term survival of children with JATD. However, their overall health-related quality of life (HRQOL) was significantly lower compared to that in healthy children. Short stature, skeletal deformities, visual impairment, as well as renal and extrarenal comorbidities, had negative impact on physical, emotional, and social functioning. The positive observation is that nearly all children attend schools with a standard education program, which is an important factor in preparing them for participation in adult life. In general, patients who underwent kidney transplantation had better quality of life than dialysis patients did. Therefore, early transplantation in those with terminal renal failure and adequate psychosocial support of the patients and their family can help to decrease the negative effects of the disease on the quality of life. Multicenter studies and use of a specific pediatric HRQOL assessment instrument are needed to develop JATD-specific interventions to optimize HRQOL.

The strengths of this study include, firstly, quite a high number of patients with similar renal phenotype, and, secondly, their long term follow-up. However, our study has limitations that should be considered. Its retrospective design may be related to potential under- and incomplete reporting, and unknown genotype of all patients.

CONCLUSION

We presented a group of JATD patients with early onset of severe renal failure, while respiratory problems were absent or mild. Long-term survival of these patients depends on renal replacement therapy. Further genetic investigations are necessary to examine whether these patients with renal phenotype share the same genotype.

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Женов синдром са бубрежном инсуфицијенцијом

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САЖЕТАК

Увод/Циљ Женов синдром (ЖС) ретка је хередитарна цилиопатија коју карактеришу асфиктична торакална дистрофија, скраћени екстремитети и прсти. Екстраскелетни поремећаји као што су хронична бубрежна инсуфицијенција (ХБИ), фиброза јетре и пигментни ретинитис пигментоза могу бити део ЖС фенотипа.

Циљ ове студије је да прикаже дуготрајно праћење ЖС болесника са раним прогресивним обољењем бубрега.

Методе Ово је ретроспективна студија педијатријских болесника са ЖС и ХБИ који су лечени на Универзитетској дечјој клиници у периоду од јануара 1980. до децембра 2014. године.

Резултати Укупно је било 13 болесника из 11 фамилија, пет девојчица и осам дечака просечног узраста 4,3 године у време дијагнозе болести. Сви болесници су имали карактеристичне промене скелета, ретиналну дегенерацију и рану ХБИ у узрасту 1,5–7 година. Пет болесника је имало неонатални респираторни дистрес и конгенитална фиброза јетре је дијагностикована код пет болесника. Један болесник је умро, док су остали преживели у току просечног праћења од 11 година. ИФТ 140 мутације су откривене у четири генетски тестирана болесника.

Закључак Просечна инциденца ЖС са реналним фенотипом у Србији је око 0,2 на милион дечје популације. Дуготрајно преживљавање ових болесника зависи од успеха терапије функције бубрега, док скелетна дисплазија, застој у расту, респираторни и очни проблеми утичу на квалитет живота.

Кључне речи: асфиктична торакална дистрофија; остеохондродисплазија; цилиопатије; неонатална респираторна инсуфицијенција; терминална бубрежна инсуфицијенција