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RESEARCH REPORT

Long-Term Systematic Monitoring of Four Polish Transaldolase Deficient Patients

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Abstract *Introduction*: Transaldolase deficiency (TALDO; OMIM 606003) is a rare inborn autosomal recessive error of the pentose phosphate pathway that, to date, has been diagnosed in 33 patients. Tżhere are few reports regarding the long-term follow-up of these patients.

The *aim* of our study is to present the disease progression in the form of a systematic long-term follow-up of four Polish patients with TALDO.

Methods and Results: We report four patients who manifested early onset TALDO. They were monitored with systematic clinical and laboratory examinations for 4–13 years. The dominant feature was an early liver injury, with subsequent renal tubulopathy. All patients presented with osteopenia and poor physical development. Our data shows that polyol concentrations seem to decrease with age.

Conclusions: In our patients, a progressive coagulopathy was the most sensitive parameter of liver dysfunction. Nodular fibrosis of the liver developed over the natural course of TALDO. This is the first report of long-term systematic clinical and biochemical monitoring of the disease progress in patients with TALDO.

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Abbreviations

AFP	Alpha-fetoprotein
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
CT	Computed tomography
GFR	Glomerular filtration rate
GSH	Reduced glutathione
HCC	Hepatocellular carcinoma
INR	International normalized ratio
IUGR	Intrauterine growth retardation
LTx	Liver transplantation
NAC	N-acetylcysteine
NADPH	Nicotinamide adenine dinucleotide phosphate
PELD	Pediatric end-stage liver disease
PLT	Platelet count
PPP	Pentose phosphate pathway
PT	Prothrombin time
TALDO	Transaldolase deficiency
TALDO1	Transaldolase gene name
US	Ultrasound

Introduction

Transaldolase deficiency (TALDO; OMIM 606003) was first described in 2001, and is a rare inborn autosomal recessive error of the pentose phosphate pathway; the initial reported patient had liver dysfunction from birth, subsequently developing liver cirrhosis at the age of 2 years (Verhoeven et al. 2001). Twenty-nine TALDO patients have

previously been diagnosed in the neonatal or early infantile period (Verhoeven et al. 2001, 2005; Loeffen et al. 2012; Valayonnopoulos et al. 2006; Wamelink et al. 2007, 2008; Tylki-Szymanska et al. 2009, 2014; Eyaid et al. 2013; LeDuc et al. 2013; Jassim et al. 2014; Al-Shamsi et al. 2015; Banne et al. 2016; Rodan and Berry 2017).

There are few reports regarding the long-term follow-up of TALDO. The oldest reported patient was diagnosed at the age of 25 years. He had already presented in childhood (exact age not available) with hepatomegaly, thrombocytopenia, and normal transaminases (Al-Shamsi et al. 2015). The first reported patient died at the age of 17 years because of liver failure (Loeffen et al. 2012). The other patient was 9 years of age at the last follow-up, presenting with liver cirrhosis, tubulopathy, and chronic kidney failure (Loeffen et al. 2012). In addition, LeDuc et al. reported the diagnosis of an 8-year-old boy with an asymptomatic presentation, identified because of HCC found in his transaldolase-deficient brother (LeDuc et al. 2013).

The aim of our study is to present the disease progression of TALDO, in the form of long-term follow-up of four Polish patients. To the best of our knowledge, this is the first reported description of such long-term clinical and biochemical monitoring of the course of TALDO.

Patients and Methods

Patients' General Characteristics

The study population consists of four boys of Polish origin, from three families; two of them were born to consanguineous parents (I and II). All the studied patients exhibited early onset of the disease. The diagnosis was established in the infantile period and was confirmed by biochemical and molecular analyses. These data were previously reported (Tylki-Szymanska et al. 2009, 2014).

In all the patients, the disorder was manifested antenatally; intrauterine growth retardation was seen in *Patients I, II,* and *III* while the presence of fluid in the pericardium and abdominal cavity in *Patient IV* was described as *hydrops fetalis*. Pregnancies of *Patients I* and *II* were associated with excessive weight gain in the mother and an unusually enlarged placenta.

In all the patients during the neonatal period, hepatosplenomegaly with coagulopathy, hypoalbuminemia, elevated transaminases, and thrombocytopenia were noted. Facial features were confirmed by the clinical geneticist as normal. Additionally, psychomotor development was assessed as normal by achievement of motor milestones at the appropriate age. Patients had characteristically thin skin with a network of visible vessels and spider angiomas. *Patients II*, *III*, and *IV* also presented with cavernous hemangiomas.

Methods of Diagnosis

Liver dysfunction, alone or combined with renal abnormalities (nephrolithiasis in *Patients III* and *IV*) prompted measurement of urinary polyols. Urinary arabitol levels and D-/L-arabitol ratio was performed using a gas chromatography method (Stradomska and Mileniczuk 2002). All identified molecular variants were prioritized according to the population frequency and the predicted effect on the protein. Pathogenic consequences were defined according to the conservation of the affected amino acids and in silico predictions.[1]

Follow-Up: Clinical and Laboratory Data

Patients were followed up with clinical and laboratory examinations approximately every 6 months from diagnosis. *Patient IV* was lost to follow-up at the age of 4 years. Therefore, the follow-up time of studied patients ranges from 4 to 13 years. Individual patients' characteristics, clinical and laboratory data are summarized in Tables 1, 2, and 3.

Clinical and laboratory data were gathered through the retrospective analysis of the patients' medical records, as well as current investigations.

Patients' Individual Characteristics

Patient I

During the neonatal period, the patient presented with a tendency toward external bleeding, abnormal coagulation profile (including prolonged INR and APTT), anemia, and thrombocytopenia. Deficiencies in factors XI and XII were diagnosed.

At the age of 1.3 years, hepatosplenomegaly with moderately elevated transaminases, clotting disturbances, cholestasis, anemia, and thrombocytopenia were noted. Abdominal ultrasound (US) revealed nodular fibrosis of the liver.

At the age of 3.5 years, *Patient I* presented with poor physical, but normal intellectual, development. He exhibited

[1] In silico prediction of the potential protein functionality of identified molecular variants was performed with: PolyPhen-2 – Polymorphism Phenotyping v2 (http://genetics.bwh.harvard.edu/pph2/index.shtml); MutationAssessor (http://mutationassessor.org); LRT – Likelihood Ratio Test (http://www.genetics.wustl.edu/jflab/lrt_query.html); SIFT – Sorting Intolerant From Tolerant (http://sift.jcvi.org/www/SIFT_BLink_submit.html); MutationTaster (http://www.mutationtaster.org/); Alamut Visual (http://www.interactive-biosoftware.com/alamut-visual/); FATHMM – Functional Analysis through Hidden Markov Models FATHMM (https://omictools.com/functional-analysis-through-hidden-markov-models-tool); MetaSVM – MetaSVM score for non-synonymous variants; MetaLR – MetaLR score for non-synonymous variants.

Table 1 Individual TALDO deficient patients' characteristics, an early onset presentation and long-term follow-up

Patient	I	II (the younger brother of I)	III	IV
Gender	Male	Male	Male	Male
Genotype	Homozygote	Homozygote	Homozygote	Compound heterozygote
	c.575G>A, p.Arg192His	c.575G>A, p.Arg192His	c.462-174_981 +53del; p.?	c.575G>A, p.Arg192His/c.462-174_981+53del; p.?
Parents' consanguinity	+	+	–	–
Pregnancy	Uneventful; excessive weight gain in the mother	Uneventful; excessive weight gain in the mother	Oligohydramnios, intrauterine growth retardation	Intrauterine growth retardation, fluid in the pericardium and abdominal cavity
Delivery, weeks	38 Unusually enlarged placenta	37 Unusually enlarged placenta	41	37
Birth weight, g	2,380	2,700	2,150	2,410
Birth length, cm	48	50	48	51
Newborn and neonatal period				
Hepatosplenomegaly	+	+	+	+
Liver function problems	+	+	+	+
Bleeding diathesis	+	+	+	+
Anemia	+	+	+	+
Thrombocytopenia	+	+	+	+
Congenital heart defects	–	–	–	–
Renal problems	–	–	–	+[a]
Developmental delay	–	–	–	–
Dysmorphia	–	–	–	–
Skin changes	+[b]	+[c]	+[d]	+[e]
Other abnormalities	+[f]	+[g]	–	+[f]
Follow-up				
Age at last evaluation (years)	13.0	10.0	7.0	4.0
Liver stiffness in FibroScan measurements at last evaluation				
Probe M, kPa	14.3	20.9	8.9	n.a.
Probe S2, kPa	18.8	62.4	n.a.	n.a.
Number of liver decompensation episodes during follow-up	2	2	None	None
Listed for liver transplantation + age of listing (years)	Yes 11.0	Yes 8.0	No	No
Age of first renal problems (years)	5.5	4.5	2.0	0.5
Renal problems at last evaluation	Tubulopathy (proteinuria, hypercalciuria, renal acidosis)	Tubulopathy (proteinuria, hypercalciuria, renal acidosis)	Nephrolithiasis tubulopathy (proteinuria, renal acidosis)	Nephrolithiasis tubulopathy (proteinuria, hypercalciuria)

+ present, – absent, *n.a.* not analyzed

[a] Recurrent urinary tract infections, at the age of 4 months few small calculi in both kidneys were found

[b] Thin skin with a visible vascular network

[c] Thin and silky skin with few cavernous *hemangiomas*

[d] Thin skin with a network of visible vessels, spider angiomas, and multiple *hemangiomas*

[e] Skin changes in the form of visibly dilated vessels, spider angiomas, and cavernous *hemangiomas*

[f] Bilateral cryptorchidism

[g] Unilateral cryptorchidism

Table 2 Laboratory and biochemical data

	Laboratory references						
Age (years)	Hb 0–2 weeks, 14.9–23.7; 2 weeks–2 months, 13.4–9.8; 2–6 months, 9.4–13; 6 months–1 year, 11.1–14.1; 1–2 years, 11.3–14.1; 2–6 years, 11.5–13.5; 6–12 years, 11.5–15.5; 12–18 years, boys, 13–16 mg/dL	PLT 150–450 × 10^3/μL	AST <52 U/L	ALT <18 months, $N < 55$/60 U/L; 18 months–12 years, boys, $N < 40$ U/L; >12 years, boys, $N < 26$ U/L	INR 0.9–1.2	AFP <5.0 IU/mL	D-/L-arabitol enantiomer ratio <3.0 mmol/mol creatinine
Patient I							
1.3	11.2–12.0	47	141–258	68–146	1.49	2,100	n.a.
3.5	12.5	80	173–190	95–136	1.52–1.87	620	14.5
5.5	10.2–11.5	59	82	44	1.34	57.4	9.15
7.5	8.2–10.4	59–71	66–132	27–40	1.31–1.45	n.a.	n.a.
10.0	11.3	83	76	36	1.48	7.5	n.a.
11.0	10.4	75	109	62	1.48	5.4	8.2
12.5	11.1	99	91	66	1.51	5.1	n.a.
Patient II							
0.1	8.6	104	55–84	66–87	n.a.	45,450	n.a.
0.4	11.2	116	94	105	1.27	21,618	13.0
1.8	8.7	78	277	113	2.08	n.a.	n.a.
4.5	10.7–11.4	83	227	82	1.60	n.a.	n.a.
6.0	10.0	155	258	80	1.56	64.1	n.a.
8.0	12.4	127	115	58	1.53	44.3	7.8
9.5	13.5	126	139	65	1.51	31.6	n.a.
Patient III							
0.1	11.2–15.9	31–125	90	72	1.88	n.a.	8.50
0.7	11.3	117	71	39	1.85	n.a.	8.37
1.0	11.1	126	133	60	1.32	49.3	n.a.
2.0	11.6	101	58	38	1.23	44.8	n.a.
7.0	11.6	106	28	16	1.10	4.62	7.5
Patient IV							
0.1	11.1	35	84–97	24–30	1.92	n.a.	n.a.
0.3	11.5	66	72	33	1.49	n.a.	n.a.
1.0	12.0	64	168	50	1.81	278	n.a.
1.4	12.6	59	163	42	1.65	n.a.	13.2
2.0	11.6	85	192	45	1.69	150	11.7
4.0	11.2	63	213	55	1.50	102	n.a.

hepatosplenomegaly, undescended testes, and thin pale skin with a visible vascular network. Thrombocytopenia and moderately elevated transaminases were still observed. Abdominal US showed disseminated small nodular changes of the liver. A gastroscopy revealed first to second degree esophageal varices, according to the Paquet classification. Elevated excretion of polyols and seven-carbon sugars was detected in the urine (Tylki-Szymanska et al. 2009). Transaldolase activity was undetectable in fibroblasts. Thus, TALDO deficiency was suspected. Molecular analysis revealed a presumed homozygous known mutation c.575G>A in exon 5 of *TALDO1* (Tylki-Szymanska et al.

Table 3 Nephrological findings in studied patients

Patient	I			II			III		IV			
Age (years)	4.0	5.5	12.0	1.0	4.5	9.0	1.0	7.0	0.6	1.8	2.5	4.0
Proteinuria	–	+	Glomerulo-tubular	–	Glomerulo-tubular	Glomerulo-tubular	–	Glomerulo-tubular	–	–	+	–
Concentration	–	n.a.	alb: 880.5 (<20)	–	alb: 21,083.3 (<20)	alb: 198.7 (<20)	–	alb: 10,290.3 (<20)	–	–	n.a.	–
LMWP, mg/g creatinine (reference range)			α1-m: 86.6 (<20) α2-m: 17.0 (<100)		α1-m: 65.5 (<20) α2-m: 28.5 (<100)	α1-m: 65.5 (<20) α2-m: 28.5 (<100)		α1-m: 314.8 (<20) α2-m: 435.5 (<100)				
Proteinuria, g/L	–	0.9	0.13	–	1.06	0.94	–	1.25	–	–	n.a.	–
Renal acidosis	–	+	+	–	+	+	–	+	–	–	n.a.	–
Glucosuria	–	–	–	–	–	–	–	–	–	–	–	–
GFR, mL/min/1.73 m^2	105	45.3	75.0	110	110.1	116.8	154.9	159.2	78.1	181.9	205.5	180.5
Serum creatinine, μmol/L	38.9	41.5	69.8	29	34.5	36.2	17.7	27.4	26.52	22.9	18.0	17.0
Calcium-creatinine ratio, Mmol/mmol (reference range <1.10)	0.99	0.33	2.32	1.04	0.95	2.85	0.27	0.60	2.03	n.a.	4.8	n.a.
Renal ultrasound	Normal	Normal	Increased echogenicity of renal parenchyma, abrogated cortex-medulla differentiation, no renal calculi	Normal	Normal	Increased echogenicity of renal parenchyma, maintained cortex-medulla differentiation, no renal calculi	Normal	Renal calculus (9 × 7 mm) in the left kidney	Bilateral renomegaly (kidney length: 6.8 and 6.5 cm) with maintained cortex-medulla differentiation and several calculi in both kidneys	Bilateral renomegaly (kidney length: 8.4 and 8.2 cm), several calculi in both kidneys (the largest in the left kidney pelvis – 1.1 cm)	Bilateral renomegaly (kidney length: 8.5 and 8.3 cm), renal calculus (1.3 cm) in the left kidney	Bilateral renomegaly (kidney length 9.0 and 9.0 cm)

LMWP low-molecular-weight-proteinuria, *alb* albumin, *α1-m* alpha-1 microglobulin, *α2-m* alpha-2 macroglobulin, + present, – absent

2009). The mutation results in the missense substitution p.(Arg192His) of a highly conserved amino acid, but there are only small physicochemical differences between arginine and histidine and this substitution does not exhibit a shift in polarity of the amino acid (Tylki-Szymanska et al. 2009).

At the age of 5.5 years, he was admitted to the hospital because of severe liver decompensation with massively increasing ascites, and palpebral and scrotal edema. Thrombocytopenia, low albumin levels requiring supplementation, slightly elevated transaminases, coagulopathy (requiring vitamin K administration), and mild proteinuria were noted.

At the age of 7.5 years, esophageal variceal bleeding occurred. He manifested convulsions, hyperammonemia, and consciousness disturbances, finally progressing to coma. Spontaneous bacterial peritonitis developed. Thrombocytopenia, hypoalbuminemia (requiring repeated albumin supplementation), moderately elevated AST, coagulopathy (requiring vitamin K administration), and proteinuria (1.25 g/L) were observed during the 2-month hospitalization. He was discharged to the pediatric hospice for palliative treatment.

At the age of 10 years, gastroscopy revealed second degree esophageal varices, requiring endoscopic ligation. The laboratory data were consistent with those noted previously.

At the age of 11 years, he was admitted to the hospital for preliminary investigations for LTx. The PELD score was 7. Hypercalciuria (calcium-creatinine ratio: 1.32 mmol/mmol), renal phosphate loss (hypophosphatemia: 0.97 mmol/L), and proteinuria (0.43 g/L) were observed.

Currently, at the age of 12.5 years, *Patient I* is in quite good clinical condition. Laboratory data show moderately elevated transaminases and slowly progressing coagulopathy (still requiring vitamin K administration). Glomerulotubular proteinuria, hypercalciuria (calcium excretion 11.7 mg/kg/day), renal phosphate loss, hypophosphatemia (0.83 mmol/L), and metabolic acidosis are present. Renal US shows increased echogenicity of the parenchyma and abrogated cortex-medulla differentiation. Fibroscan measurements reveal moderately increased liver stiffness (Table 1). His psychomotor development is normal; however, he is presenting with osteopenia and poor physical outcomes, measuring in the <3rd percentile for both height-for-age and weight-for-age. He is qualified for hormonal studies because of cryptorchidism (results are pending).

Patient II

Since delivery, *Patient II* suffered bleeding diathesis (with the same coagulation profile as *Patient I* with deficiencies in factors XI and XII), severe anemia, thrombocytopenia, and slightly elevated transaminases. A thin, silky skin with cavernous hemangiomas and unilateral cryptorchidism were noted.

At the age of 5 months, hepatosplenomegaly was observed. Abdominal US revealed a homogeneous liver parenchyma. Anemia, moderately elevated transaminases, cholestasis, and bleeding diathesis were noted. Diagnostics of TALDO deficiency was commenced as a part of familial screening. Polyols and seven-carbon sugars were elevated (Tylki-Szymanska et al. 2009). Molecular analysis revealed the same genotype as in *Patient I* (Tylki-Szymanska et al. 2009).

At the age of 1.8 years, *Patient II* presented with anemia, progressive thrombocytopenia, coagulopathy (requiring vitamin K administration), moderately elevated transaminases, and cholestasis. Abdominal US revealed nodular fibrosis.

At the age of 4.5 years, he was admitted to the hospital due to severe liver decompensation, presenting with massively increasing ascites and scrotal edema. Thrombocytopenia, coagulopathy (requiring vitamin K administration), moderately elevated transaminases, cholestasis, and hypoalbuminemia (requiring albumin supplementation) were noted. Gastroscopy revealed first degree esophageal varices, according to the Paquet classification. Tubulopathy was noted for the first time (Table 3).

At the age of 6 years, *Patient II* was in good clinical condition, but had anemia, moderately elevated AST, and slightly elevated ALT, hypoalbuminemia (still requiring albumin supplementation) and coagulopathy (requiring vitamin K administration). A gastroscopy revealed first degree esophageal varices.

At the age of 8 years, he was admitted to the hospital for preliminary investigations for LTx. Progressive thrombocytopenia, moderately elevated AST, and slightly elevated ALT, coagulopathy (requiring vitamin K administration), and cholestasis were noted. The PELD score was 12. Abdominal US revealed a small liver with strongly heterogeneous parenchyma.

Currently, at the age of 9.5 years, *Patient II* is in a satisfactory clinical condition. Laboratory data show moderately elevated AST, slightly elevated ALT, and progressive coagulopathy (still requiring vitamin K administration). Glomerulo-tubular proteinuria, hypercalciuria (calcium excretion 13.3 mg/kg/day), renal phosphate loss (hypophosphatemia 0.97 mmol/L), and metabolic acidosis are present. Renal US shows increased echogenicity of the parenchyma and abrogated cortex-medulla differentiation. Fibroscan measurements reveal highly increased liver stiffness (Table 1). His psychomotor development is normal. He has osteopenia: 10–25th percentile, height-for-age; and <3rd percentile, weight-for-age.

Patient III

Clinical and laboratory examinations in the first days of life revealed progressive anemia, thrombocytopenia, and an abnormal coagulation profile (including prolonged INR and APTT). Like *Patients I* and *II*, deficiencies in factors XI and XII were diagnosed.

At the age of 1 month, *Patient III* was hospitalized because of hepatosplenomegaly and failure to thrive. Thin skin with a network of visible vessels, spider angiomas, and multiple hemangiomas were observed. Anemia, thrombocytopenia, slightly elevated transaminases, and bleeding diathesis were still noted. Sugars and polyols were measured, revealing elevated excretion in the urine (Tylki-Szymanska et al. 2014). A homozygous deletion c.462-174_981+53del in the *TALDO1* gene was identified. This deletion spans 1,317 bps and alters the acceptor splice site of exon 5 (Tylki-Szymanska et al. 2014).

At the age of 12 months, he presented with hepatosplenomegaly, moderately elevated AST and slightly elevated ALT, coagulopathy (as previously diagnosed, requiring vitamin K administration), and hypoalbuminemia (requiring albumin supplementation).

Patient III was diagnosed at the age of 2 years with nodular fibrosis of liver. Additionally, a small calculus in the left kidney was found. Laboratory data showed anemia and coagulopathy (requiring vitamin K administration).

Currently, at the age of 7 years, *Patient III* exhibits mild hepatosplenomegaly, and nephrolithiasis of the left kidney. On physical examination, hemangiomas and telangiectasias of the skin are present. Laboratory data show anemia and thrombocytopenia. Fibroscan measurements reveal mildly increased liver stiffness (Table 1). Nephrological studies show glomerulo-tubular proteinuria (Table 3). *Patient III*'s mental development is normal; he is presenting with osteopenia: 25th percentile, height-for-age; and 3rd percentile weight-for-age.

Patient IV

Clinical examination in the first days of life showed splenomegaly and bilateral cryptorchidism. Anemia, thrombocytopenia, coagulopathy (including abnormal INR), and mildly elevated AST were noted.

At the age of 4 months, *Patient IV* presented with hepatosplenomegaly, anemia and thrombocytopenia, moderately elevated AST, and bleeding diathesis. Abdominal CT showed small calculi in both kidneys.

Recurrent urinary tract infections were noted from birth. At the age of 7 months, hypercalciuria (calcium excretion 7.57 mg/kg/day) was noted. Renal US showed bilateral renomegaly with maintained cortex-medulla differentiation and several calculi in both kidneys.

At the age of 12 months, he presented with hepatosplenomegaly, anemia and thrombocytopenia, moderately elevated AST, and bleeding diathesis.

At the age of 15 months, urinary sugars and polyols were measured, and the profile suggested TALDO deficiency (Tylki-Szymanska et al. 2014). Molecular analysis revealed two mutations (c.575G>A, c.462-174_981+53del) in the *TALDO1* gene. Each parent was identified as a carrier of one of these mutations, confirming their biallelic distribution (compound heterozygosity) in the child (Tylki-Szymanska et al. 2014).

At the age of 2 years, thrombocytopenia, moderately elevated AST, and coagulopathy (requiring vitamin K administration) were present. Abdominal US revealed hepatosplenomegaly with heterogeneous liver parenchyma (nodular fibrosis), bilateral renomegaly, and several calculi in both kidneys.

At the age of 2.5 years, *Patient IV* sustained a head injury with severe subcutaneous bleeding requiring transfusion of large amounts of platelet concentrates and fresh frozen plasma. Urine analysis revealed proteinuria, extremely high hypercalciuria (calcium-creatinine ratio: 4.8 mmol/mmol).

At the age of 3 years, ureterorenoscopic lithotripsy was undertaken. The patient was lost to follow-up after the age of 4 years, at which time he presented with hepatosplenomegaly, bilateral renomegaly, thrombocytopenia, progressive coagulopathy (requiring vitamin K administration), and moderately elevated AST.

Discussion

Clinical Presentation and Systematic Monitoring

All our patients presented with early onset TALDO. *Patients I* and *II* suffered from severe liver dysfunction from birth, subsequently developing liver fibrosis and cirrhosis. The first renal manifestations, in the form of tubulopathy, were noted at the age of 4.5 and 5.5 years, respectively. In *Patients III* and *IV*, a milder hepatic phenotype (without liver decompensation episodes) was observed, probably due to the earlier (fetal) development of liver fibrosis. The first renal abnormalities were manifested earlier, at the age of 2 and 6 months, respectively, in the form of nephrolithiasis and tubulopathy.

Most of the patients described in the literature presented with severe symptoms in the neonatal period (Verhoeven et al. 2001, 2005; Loeffen et al. 2012; Valayonnopoulos et al. 2006; Wamelink et al. 2007, 2008; Tylki-Szymanska

et al. 2009, 2014; Eyaid et al. 2013; LeDuc et al. 2013; Jassim et al. 2014; Al-Shamsi et al. 2015; Banne et al. 2016; Rodan and Berry 2017). Reports from the literature and our observations suggest the existence of two main presentations of TALDO: an early onset presentation (prenatal or neonatal disease) which constitutes a severe form, in most of the cases rapidly fatal, and a late onset presentation (early or late infantile form) which comprises a slowly progressive form of the disease with favorable long-term outcome.

In both early and late onset presentations, liver dysfunction begins in early fetal life. In the early onset presentation, liver disease is manifested in the form of clotting disturbances, elevated transaminases, hypoalbuminemia, and skin changes in newborns. Progressive liver failure then leads to reduced lifespan. In patients with later onset of symptoms, liver dysfunction progresses more slowly, with liver fibrosis and cirrhosis developing.

The kidneys are affected in TALDO in the form of renal tubular dysfunction (Loeffen et al. 2012). The earliest laboratory findings in our patients were hypercalciuria and proteinuria. Clinical examinations revealed features of osteopenia, as a consequence of tubulopathy. In the most severe cases, a generalized proximal tubulopathy, renal Fanconi syndrome, may develop. Loeffen et al. (2012) reported that, among nine patients with TALDO, aging from 1 year to adolescence, seven had proteinuria, glucosuria, aminoaciduria, hypercalciuria, nephrocalcinosis, metabolic acidosis, complete renal Fanconi syndrome, and moderate chronic kidney disease. The earliest and most prevalent finding of kidney disease was low molecular weight proteinuria (Loeffen et al. 2012).

Renal phenotype is most commonly manifested later than liver dysfunction, although in our *Patients III* and *IV*, and other patients from the literature, renal abnormalities were also manifested in early infancy (Loeffen et al. 2012).

TALDO also presents with skin manifestations (Verhoeven et al. 2001, 2005; Loeffen et al. 2012; Valayonnopoulos et al. 2006; Wamelink et al. 2007, 2008; Tylki-Szymanska et al. 2009, 2014; Eyaid et al. 2013; LeDuc et al. 2013; Jassim et al. 2014; Al-Shamsi et al. 2015; Banne et al. 2016; Rodan and Berry 2017). Telangiectasias are related to significant damage of the liver. Hemangiomas observed in our *Patients II*, *III*, and *IV*, and other patients are probably secondary to disturbed placental formation and function (Verhoeven et al. 2001, 2005; Loeffen et al. 2012; Valayonnopoulos et al. 2006; Wamelink et al. 2007, 2008; Tylki-Szymanska et al. 2009, 2014; Eyaid et al. 2013; LeDuc et al. 2013; Jassim et al. 2014; Al-Shamsi et al. 2015; Banne et al. 2016; Rodan and Berry 2017). Nonetheless, cutis laxa or hypertrichosis described by other authors was not present in our patients.

The patients described in this report presented with normal facial features. As most (79%) of the children reported with TALDO were the offspring of consanguineous parents (including 12 patients from one Arabian tribe) (Verhoeven et al. 2001, 2005; Loeffen et al. 2012; Valayonnopoulos et al. 2006; Wamelink et al. 2007, 2008; Tylki-Szymanska et al. 2009, 2014; Eyaid et al. 2013; LeDuc et al. 2013; Jassim et al. 2014; Al-Shamsi et al. 2015; Banne et al. 2016; Rodan and Berry 2017), dysmorphic features should be described by a clinical geneticist/dysmorphologist and should be similar in related patients.

Pathogenesis and Biochemical Monitoring

The pathogenesis of liver and kidney diseases in TALDO is most probably a toxic impact of the accumulated sugars and polyols on the hepatocytes and kidney tubules (Loeffen et al. 2012). The formulation of the PPP without TALDO leads to the accumulation of sedoheptulose-7-phosphate, ribose-5-phosphate, ribulose-5-phosphate, xylulose-5-phosphate and C5-polyols: D-ribitol; D-arabitol; and D-xylitol (Perl et al. 2006; Perl 2007). The polyol concentrations are probably the highest in the neonatal period (LeDuc et al. 2013). Our data shows that polyol concentrations seem to decrease with age (Table 2).

To our knowledge this is the first description in the literature regarding such a long-term monitoring of biochemical studies in patients with TALDO.

Treatment

There is no effective treatment for TALDO. LTx at an early stage of the disease could perhaps be useful but some authors hypothesize that disease recurrence is a risk (LeDuc et al. 2013; Al-Shamsi et al. 2015). Only one child with TALDO has been reported to have undergone liver transplantation (at the age of 1 year) and was followed up; the patient was doing well at the age of 3 years with normal coagulation profile and slightly elevated transaminases (Al-Shamsi et al. 2015).

All our patients were treated symptomatically. *Patients I* and *II* were listed for LTx at the age of 11 and 8 years, respectively, but they are currently disqualified from such treatment due to their overall satisfactory condition.

Recently, Rodan et al. described a case of TALDO in an infant, who manifested with multisystem disease and was treated with NAC for 6 months (Rodan and Berry 2017). The authors concluded that this supplementation probably helps to normalize AFP levels and could result in decreased hepatocyte injury. The data from our patients show that AFP levels normalized with age.

Conclusions

TALDO manifested in our patients as an early onset disorder. The dominant feature was an early liver injury with subsequent renal abnormalities in the form of tubulopathy. Progressive coagulopathy is a sensitive parameter indicating liver dysfunction in TALDO.

Despite the severe phenotype, the patients remain in a relatively good clinical condition.

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