PLURIMALFORMATIVE SYNDROME – CASE REPORT

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Abstract

Complete situs inversus is a genetic disorder with autosomal dominant, autosomal recessive or X-linked transmission, part of the group of ciliopathies and the subgroup of primary ciliary dyskinesias. We present the case of a 3 years and 8 months old girl, who associates complete situs inversus to chronic renal failure – left vesicoureteral reflux with secondary hydronephrosis, hypoplastic ectopic right kidney, hydrocephaly, bilateral varus equine foot and failure to thrive. She was first admitted in our hospital at 3 weeks of age and followed-up since then, necessitating complex medical and surgical therapy: treatment of recurrent urinary tract infections, surgical treatment of the VUR - terminal ureterostomy at 9 month, surgical treatment of the hydrocephaly – Medtronic – Delta valve – at 1 year and 6 month, surgical treatment of the varus equine foot at 3 years, nutritional and neurological recovery. The particularity of this case resents in the association of multiple malformations with a bad prognosis, because of progression of the renal failure and of the neurological impairment. She needs a complex follow-up with the collaboration of the paediatric nephrologist, paediatric surgeon, paediatric neurologist, brain surgeon and family doctor.

Key words: ciliopathies, situs inversus, hydronephrosis, hydrocephaly, child.

Introduction

Cilia are cellular organites with micro tubular structure, which are present on the surface of the majority of the human cells. Although they were described for the first time in 1853 (Purkinje and Valentin), the most discoveries related to their structure and function were made in the last 10 years. During almost 200 years cilia became from simple vestigial organites, cellular “antenna” that mediate a multitude of signalization ways.

Studies regarding cilia led to the definition of ciliopathies, a pathogenic group whose etiology is based on defects in the genesis, structure and/or function of the cilia, characterized by important genotypic and phenotypic heterogeneity.

Case report

Anamaria I., 3 years and 8 month old, first admitted in January 2007 and followed up since then in the Paediatric Clinic I, Children’s Hospital “Louis Turcanu” Timisoara, is the first child of a mother who worked in a toxic environment in the first 3 month of pregnancy. She was born premature (31 weeks gestational age), Apgar score = 7, birth weight = 2200 g.

History reveals a first admission to the hospital at 3 weeks of age, transferred from the County Hospital Arad to the Premature Department of our hospital with the following diagnoses: Acute renal failure. Urinary tract infection with Candida albicans. Left knee osteoarthritis with Candida albicans. Complete situs inversus. Bilateral hydrenephrosis. Bilateral varus equine. Intraventricular hemorrhage grd. II. Neonatal seizures, prolonged admission until 3 month of age with a slow favorable course. She presented 2 more episodes of urinary tract infection with E coli at 4 and 6 month of age, and imaging was performed: cystourethrography showed massive left vesicoureteral reflux (VUR) with grd. IV hydrenephrosis, urography confirmed the left hydrenephrosis and showed an ectopic pelvic right kidney with delayed, poor secretion after 3 hours; renal scan using 99mTc-labeled dimercaptosuccinic acid (DMSA) revealed a normal sized left kidney with poor excretion and stasis and a pelvic right kidney with reduced capture and excretion, relative function 27%-right kidney and 73%-left kidney. At 9 month of age she was admitted to the Paediatric Surgery Clinic, Children’s Hospital ”Louis Turcanu” Timisoara for the surgical treatment of the vesicoureteral reflux – terminal ureterostomy. From May 2006 until January 2007, the patient was non-compliant to follow-up and therapy.

The patient was first admitted to our clinic with fever, unrest, disuria, failure to thrive. Physical examination revealed weight = 5600 g, height = 64 cm, cranial circumference = 47 cm (all parameters under 3rd percentile), temperature = 38,2°C, pallor, normal respiratory findings, HR = 98/min, BP = 90/60 mm Hg, permeable ureterostomy in the left iliac fossa, normotensive anterior fontanella, spastic hypertonia of the legs, motor retardation, bilateral varus equine. Biological findings showed positive inflammatory markers, GFR = 38,26ml/min/1.73m2, leucocyturia and negative urine culture (urine collection after initiation of antibiotherapy).

Abdominal ultrasound: situs inversus, liver (left) with normal structure, left hepatic lobe = 76,7mm, portal vein = 7,16 mm, spleen (right) with normal structure, long axis = 64 mm, left kidney with irregular shape and contour, 58,3/36,3 mm, pelvic dilation of 22,6/9,67 mm, grd. II hydrenephrosis, right kidney undetectable, bladder with normal walls. (Fig. 1)
Cardiac ultrasound: atrioventricular and ventriculoarterial concordance, mitral and tricuspidian grd. I regurgitation, normal origin of the coronary arteries, right aortic arch, descendent aorta on the right side of the spine, situs inversus totalis.

EKG: normal sinusal rhythm, 130/min, QRS axes 130°, indirect signs of right ventricular hypertrophy, aspect of dextrocardia.

Recurrent urinary tract infections were the reason for completing imaging in this case and an abdominal MRI was performed (February 2007), which revealed: complete situs inversus, liver on the left and spleen on the right side, right position of the heart, left kidney with normal position, 5,8/3 cm, with preserved function and pyelocalyceal hypotonia, right kidney ectopic, anterior of the sacral vertebrae, 4/2,1 cm. Conclusion: complete situs inversus, ectopic right kidney. (Fig. 2)

Neurological impairment was the reason for a complete neurological assessment: Electroencephalogram, ultrasonography and cerebral MRI (02.2007), which showed an active tetra ventricular hydrocephaly. (Fig. 3)

Correlating the clinical, biological and imagistic data, the following diagnosis was established:
- Left vesicoureteral reflux with secondary grade II hydronephrosis
- Hypoplastic ectopic right kidney
- Recurrent urinary tract infection
- Chronic renal failure stage II
- Complete situs inversus
- Active hydrocephaly
- Recurrent seizures
- Failure to thrive
- Bilateral varus equine

Fig. 1: Abdominal ultrasound.

Fig. 2: Abdominal MRI.
Medical therapy consisted in antibiotics: Cephrtriaxone 100 mg/kg/day, iv, 7 days, followed by prophylaxis with Nitrofurantoin 2 mg/kg/day once daily, and symptomatic treatment: antiemetic, antipyretic, anticonvulsive medication and vitamins (D, group B). Surgical therapy of hydrocephaly, consisting in ventricular-peritoneal drainage with Medtronic – Delta valve, was performed (February 2007). Diet recommendations were: caloric intake of 120 kcal/kg, aprox. 100% RDA for age, protein intake 0.6 – 0.8 g/kg/day – 100 – 120% RDA, supplementation with essential amino acids and ketoacids, phosphate restriction and no fluid restriction.

Clinical course was initially favorable, she still presented until now 2 -3 episodes of urinary tract infection/year, explained by particular factors such as – complex urinary tract malformation, presence of ureterostomy, secondary immune deficiency – chronic renal failure is characterized by lymphopenia, inappropriate response of polymorphonuclear cells to bacterial infection and insufficient Fc receptors on the macrophages and malnutrition by atrophy of lymphatic organs, depletion of LT, L NK, reduction of bactericidal activity of polymorphonucleares, low levels of secretor IgA, alteration of complement system. Surgical treatment of varus equine was performed July 2008.

Possible complications are those of VUR: renal scars, hypertension (aprox. 10% of the children with renal scars), chronic renal failure (in USA 8,4% of the cases with chronic renal failure are due to reflux nephropathy) and urolithiasis (19,1 – 29,8 %, after Millnier et al., hypercalcuiuria present in over 50% of the children with VUR being a risk factor) and those due to long time administration of antibiotics: rush, hepatic toxicity, medullar toxicity, antibiotic resistance. Situs inversus per se has no complications but can be associated in 5 – 10% with cardiac anomalies (transposition of great vessels), especially when situs inversus is incomplete (up to 95%).

Short time prognosis of the urinary tract infections is good, long time prognosis depends on the frequency of the recurrent infections, progressive evolution of renal failure and neurological impairment.

The case needs a complex follow-up with the collaboration of the paediatric nephrologist, paediatric surgeon, paediatric neurologist, brain surgeon and family doctor.

**Discussions**

The case is particular due to the complex plurimalformative syndrome: the literature mentions the association between situs inversus and hydrocephaly, the association between situs inversus and renal anomalies such as renal dysplasia/hypoplasia/tumors but not the association between all three elements.

VUR is considered the most frequent malformative uropathy of the child. The prevalence in the healthy population is unknown, the incidence is 1,3% after Ransley 1 and between 29 – 50% in the population with urinary tract infections, with a higher rate in girls.

Renal hypoplasia is frequent unilateral, with a higher frequency in boys, with an incidence of 1/300 newborns, is often associated to VUR. 2 Clinical forms: renal dysplasia, aplasic type (loss of cortical and medullar structure, histopathologic diagnosis), ischemic small kidney (hypoplasia of the renal artery, history of high blood pressure) and small pyelonephrytic kidney (history of recurrent pyelonephritis).3 Ectopic kidneys are associated in 25 – 70% of the cases with VUR.

Complete situs inversus was first described in 1793 by Baillie. It is a ciliopathy, with autosomal dominant, autosomal recessive or x-linked transmission.

In the embryonic stage of gastrula the clockwise rotation movement of the nodal cilia (mobile, structure 9+0) determines an extra cellular fluid flux towards the left side and implicit.
the left – right asymmetry. The anomalies of these cilia are implicated in the generation of complete situs inversus and situs ambiguous (polisplenia, agenesia of the spleen, annular pancreas, horseshoe kidney etc.).

Primary ciliary diskinesias are a heterogeneous group of disease, 90% show structural changes of the outer-arm or inner-arm of dynein. They are the result of defects of the mobile cilia (structure 9+2). The mobile cilia contain over 250 proteins with structural and/or functional role. Any defect at any of these proteins generates motility anomalies (hyper motility, hypo motility, asynchronism) and consequently the reduction of the mucociliary clearance. Clinical implications can be the appearance of recurrent or chronic respiratory infections, hydrocephaly, and fertility problems. Primary ciliary diskinesia is associated in 50% of the cases with situs inversus, association known as Kartagener syndrome. In this case the mutation is on the gene DNAH 11 (7p21) – motor subunit of dynein, "left-right dynein", responsible for the rotation movements of the cilia of ciliar cells of Hensen nodule. (Fig. 4)\(^5\)

Other ciliopathies are generated by defects of the primary cilia (structure 9+0, immobile). These are receptors for a multitude of signalization ways, which maintain the cellular homeostasis. Impossibility of maintaining this homeostasis determines the appearance of polycystic kidney disease, as well as of some syndromes that can associate retinitis pigmentosa, impaired sense of smell, obesity, diabetes, hypertension, mental retardation: Senior-Lokren syndrome, Joubert syndrome, Biedl-Bardet syndrome.\(^6\)

It seems that the neural tube defects appear too as a consequence of primary cilia anomalies, there also are several syndromes unidentified yet.\(^7\)

The association situs inversus – hydrocephaly was first mentioned in the literature by Greenstone in 1984. In 2002 Tallon et al demonstrated in mice that the mutation of the gene Mdnah 5 (chromosome 15) generates the absence of the outer-arm of dynein and clinic situs inversus and hydrocephaly in all cases.\(^8\) Hydrocephaly is the consequence of ependimary cilia alterations as part of the primary cilia dysfunction. There also is demonstrated (2007, a 5 children study group) that the mutation of the gene 1p 31.3, which encodes the nuclear transcription factor IA (NFTIA) is associated to central nervous system anomalies such as agenesia of corpus callous + hydrocephaly + ventriculomegaly + Chiari type 1 malformation + “tethered spinal cord” + VUR.\(^9\)

Early development of chronic renal failure (reflux nephropathy) in this case is due to the coexistence of several risk factors: recurrent urinary tract infections and renal scars, association with other renal anomalies, low birth weight, neurological impairment.

References
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Fig. 4: Structure 9+2.

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