Rare case of nephrotic syndrome: Schimke syndrome

Caso raro de síndrome nefrótica: síndrome de Schimke

Authors
Anna Kelly Krislane de Vasconcelos Pedrosa [1,2]
Luiz Fernando Oliveira Torres [1]
Ana Corina Brainer Amorim da Silva [3]
Adrianna Barros Leal Dantas [4]
Káthia Liliane da Cunha Ribeiro Zuntini [1,4]
Lia Cordeiro Bastos Aguiar [5]

[1] Universidade Estadual do Ceará.
[2] Hospital Infantil Albert Sabin.
[3] Hospital Geral Waldemar de Alcantara.
[4] Universidade de São Paulo.
[5] Universidade Federal de São Paulo

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Correspondence to:
Anna Kelly Krislane de Vasconcelos Pedrosa.
Universidade Estadual do Ceará.
Rua Moreira Gomes, nº 795, Vila União, Fortaleza, CE, Brazil.
CEP: 60410-722
E-mail: krislanekkv@gmail.com

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Abstract

Schimke syndrome corresponds to dysplasia of bone and immunity, associated with progressive renal disease secondary to nephrotic syndrome cortico-resistant, with possible other abnormalities such as hypothyroidism and blond marrow aplasia. It is a rare genetic disorder, with few reports in the literature. The most frequent renal involvement is nephrotic syndrome with focal segmental glomerulosclerosis and progressive renal failure. The objective of this study was to report a case of Schimke syndrome, diagnostic investigation and management of the case.

Keywords: immunologic deficiency syndromes; osteochondrodysplasias; nephrotic syndrome.

Resumo

A síndrome Schimke corresponde à displasia imuno-óssea, associada à doença renal progressiva secundária à síndrome nefrótica córtico-resistente, podendo haver outras anormalidades como hipotireoidismo e aplasia de medula óssea. Trata-se de uma patologia genética rara, com poucos relatos na literatura. O acometimento renal mais frequente é uma síndrome nefrótica por glomeruloesclerose segmentar e focal e falência renal progressiva. O objetivo deste estudo foi relatar um caso de síndrome de Schimke, investigação diagnóstica e condução do caso.

Palavras-chave: osteocondrodisplasias; síndrome nefrótica; síndromes de imunodeficiência.

Introduction

Schimke immuno-osseous dysplasia (SIOD) was first described in 1971 by Schimke, characterized by spondyloepiphyseal dysplasia, T-cell immunodeficiency and progressive kidney disease with nephrotic proteinuria.[1]

SIOD is an autosomal recessive disorder. There are approximately 50 cases described in the literature so far, there is no association with gender, ethnicity and geographic location. The exact disease prevalence is still unknown.[2]

Clinical evidence of SIOD are: spondyloepiphyseal dysplasia causing growth disorders, typical facies, nephrotic syndrome caused by focal segmental glomerulosclerosis (FSGS) and progressive renal failure, recurrent lymphopenia, T-cell immunodeficiency and pigmented nevi.[2] Other findings include: hypothyroidism, transient cerebral ischemia and bone marrow aplasia. The literature also suggests an association with dental malformations, neurological complications such as chronic headache, autoimmune diseases and cancer, including non-Hodgkin's lymphoma and osteosarcoma.[3,4]

Case report

Female, 9 years old, brown, born at Boa Viagem-CE, healthy parents and sister, with no history of consanguinity.

Uneventful maternal and obstetric histories. Obstetric ultrasound showed no malformations. The child was born from a cesarean section because of severe oligohydramnios and preterm labor in January 2006. She was small for her gestational age (36 weeks, weighing 1,750 kilograms). No malformation was diagnosed on her examination as a newborn.

Her mother said there were no complications in her first days of life. Her newborn screening proven unchanged for congenital hypothyroidism (TSHn: 2.70 IU/L) and phenylketonuria (PKU: 1.6 mg/dL). Childcare held irregularly in primary care in the city of Boa Viagem. Adequate food history at all stages of life.

She had psychomotor development milestones at the appropriate times, but since 5 months of age, her mother realized she was underweight and of low height for her age. It was only at 2 years of age that she was alerted of growth retardation. Up to 2 years of age she had had only common childhood infections. Between 2 and 4 years of age, he had three severe infections with hospital stay in two of them.

In July of 2010 (4 years old), during hospitalization in the municipality of origin because of a community-acquired pneumonia, she was diagnosed with important growth retardation and low weight gain (9.7 kg and 72 cm → below the 3rd percentile). The following month, the child was then referred to the Endocrine-pediatrics clinic of the Albert Sabin Children's Hospital (HIAS) in Fortaleza-CE. On physical examination she was on pubertal stage M1P1, no palpable thyroid, Olympian forehead, thin and sparse hair and pectus carinatum. Height and weight standard deviations: -7. Normal psychomotor development. Her thyroid ultrasound showed a reduction in diffuse echogenicity of the thyroid parenchyma. Bone age X-rays suitable for her age. For her initial laboratory tests, see Chart 1.

She was diagnosed with hypothyroidism and nephrotic syndrome; treatment was started with levothyroxine and she was referred to the Nephro-pediatrics and Genetics Services (December 2010) to investigate disproportion between trunk and limbs associated with syndromic facies (hypertelorism, diffuse alopecia, low ear implantation). We suspected of TSH change secondary to nephrotic syndrome. She was later diagnosed with bone dysplasia (disproportion in limb-to-trunk length, flattened vertebrae and dysplastic femoral epiphysis).

In December of 2010, she developed nephrotic syndrome, hypertension and estimated creatinine clearance (Schwartz) pointing to stage II chronic kidney disease (76.4 ml/min/1.73 m²). She was submitted to steroid therapy for five months, and she was steroid-resistant. A renal biopsy was carried out (May 2011), showing focal segmental glomerulosclerosis (5/31) - FSGS and focal tubular atrophy with mild interstitial fibrosis.

She was given oral cyclosporine and prednisone between September 2011 and August 2012, intermittently due to infectious processes. The treatment was suspended because of persistent neutropenia, maintaining massive proteinuria and progressive loss of renal function. He remained in outpatient treatment using angiotensin converting enzyme (ACE) inhibitors, diuretics (spironolactone and thiazide), beta-blockers and statins, as well as conservative measures for chronic kidney disease.[4]

In December 2012, her estimated creatinine clearance (Schwartz) = 27.8 ml/min/1.73 m² and ultrasonography showed diffusely reduced kidney size and loss of corticomedullary differentiation.

We investigated recurrent infections (six episodes of community-acquired pneumonia - five severe ones and one case of acute suppurative otitis media and three severe episodes of herpes zoster within one year) using the Immunology department, which showed immune deficiency of T, B and NK cells as per shown on Chart 2.

We then established a clinical diagnosis of Schimke syndrome in February 2013. The patient presented with hypothyroidism, bone dysplasia (disproportion in limb-to-trunk length, flattened vertebrae and dysplastic femoral epiphysis), immunodeficiency, unwieldy steroid-resistant nephrotic syndrome and syndromic phenotype. Other organs and body systems investigated were normal. We did not perform genetic testing because it was not available.

She evolved with rapid loss of renal function (estimated creatinine clearance in September 2014: 13 ml/min/1.73 m²-Schwartz) and was submitted to kidney transplant in November of 2014.

Currently, the patient remains with normal renal function (estimated creatinine clearance in April 2015: 104.5 ml/min/1.73m²- Schwartz) without nephrotic syndrome recurrence and with thyroid function control (TSH: 2.47 and FreeT4: 1.7). She had a severe infection (Epstein Baar virus encephalitis) and ischemic stroke in 2015, without sequelae.

Discussion

The SIOD phenotype can vary from severe to mild, according to onset being *in utero* or late.[2] The only known cause is the mutation in the SMARCAL 1 gene, HepA-related protein; however, approximately 50% of patients do not have this mutation.[5]

Chart 1 Tests upon admission, 2010

Test	Value	Reference	Units
TSH	6.8	07-6.0	mUI/L
FreeT4	20.76	12-22	pmol/L
AntiTG Antibody	26.7	< 40.0	IU/mL
AntiTPO Antibody	8.12	< 35.0	IU/mL
Cortisol (morning)	232.1	Morning: 171-536 Afternoon: 64-327	nmol/L
PTH	19.9	12.0-72.0	pg/mL
Albumin	2.6	3.5-5.5	g/dL
GH	4.19	< 10	ng/mL
IGF-1	< 25ng/ml	4 years: 49-283 5 years: 50-286	ng/ml
IGFBP-3	2.32	4 years: 1 - 4.7 5 years: 1.1 - 5.2	µg/mL
IgA	125	15-250	mg/dL
IgG	700	340-1600	mg/dL
IgM	115	45-300	mg/dL
Calcium	8.1	8.4 to 10.5	mg/dL
Phosphorus	5.6	2.5 to 5.6	mg/dL
Potassium	4.5	3.5-5.0	mmol/L
Urea	14	10-50	mg/dL
Creatinine	0.4	0.3 a 0.4 (adapted for the child's height)	mg/dL
Urine summary	Proteinuria (+++)	Absent	
24h Proteinuria	548.07	20-150	mg/dL
24h Proteinuria	56.4	Normal < 5 Mild/Moderate 5-50 Massive > 50	mg/Kg/dia
Triglycerides	417	Desirable < 150 Threshold: 150-199 High: 200-499 Very high > 500	mg/dL
Total cholesterol	216.29	Excellent < 150 Threshold: 150-169 High > 170	mg/dL

Source: the authors.

Chart 2 Immune investigation tests, 2012

Test	Value	Conclusion
T-cells immunophenotyping	T cells (CD3): 88.48% 1660/mm³ B cells (CD19): 9.01% 169/mm³ NK cells (CD56): 2.51% 47/mm³ *T cells* CD 4: 10.55% 175/mm³ CD8: 85.24% 1415.mm³ CD4/CD8 ratio: 0.16% 3/mm³	Normal → very low p10: 217 → very low p10: 618 → very low p90: 1024 → altered Normal: 0,1: 1 → altered
IgA	171	p50: 127
IgG	545	
IgM	103	p50: 86
IgE	6.14	p10: 10

Source: the authors.

SMARCAL 1 is a fundamental remodeling protein for genome integrity. Deficient SMARCAL 1 cells show collapsed replication forks, cell cycle arrest in S phase, chromosomal instability and genomic hypersensitivity to toxic agents, changing cellular sensitivity to the replication infecting agents.[6]

The nephrotic syndromes caused by genetic disorders are associated with mutations in the glomerulus structural proteins, thereby altering its permeability. It is characterized by: early presentation, low response rate to treatment and recurrence after transplantation. However, each mutation, has a different spectrum of disease and severity. Most are resistant to steroids; however, some forms present less early, and these have good response to immunosuppressive therapy, its use should be considered individually.[7]

In developing fetal kidneys, the SMARCAL1 gene is expressed in the ureteric epithelium, stroma metanephric mesenchyme, and in all nephron development stages. In postnatal kidneys, the SMARCAL1 is expressed in nephron's epithelial tubules, collecting tubules and glomeruli (podocytes and endothelial cells). Studies suggest that disruption in genomic integrity during fetal kidney development contribute to the pathogenesis of FSGS in patients with SIOD.[8]

There are reports of partial proteinuria improvement with use of cyclosporine in steroid-resistant nephrotic syndrome, even associated with genetic disease, and some non-immunosuppressive mechanisms have been proposed: vasoconstriction of the afferent arterioles and loss of albumin reduction by changing the glomerular filtration rate.[9,10] However, the use of cyclosporine is contraindicated in patients with advanced degree of tubular atrophy and interstitial fibrosis in kidney biopsy,[11] and its use is also viewed with caution due to lymphopenia and recurrent infections.

SIOD's nephrotic syndrome does not usually respond to treatment with steroids, but there are reports of transient improvements in proteinuria using ACEI, renin-angiotensin channel blockers (RAB) and cyclosporine. In more severe cases of nephrotic syndrome and/or end-stage chronic renal failure stage, renal transplantation is indicated and there are no reports of post-transplant nephrotic syndrome, although infectious and cerebrovascular complications can still occur, since the SMARCAL mutation affects many systems beyond glomeruli.[2] There is no consensus as to bone marrow transplantation as treatment for marrow involvement.[12]

It has been reported that patients with SIOD generally die within the first two decades of life by: infections (23%), stroke (17%), renal failure (15%), pulmonary hypertension and congestive heart failure (15%), organ transplant complications (9%), complications of lymphoproliferative diseases (9%), gastrointestinal hemorrhage (6%), bone marrow aplasia (3%) and acute restrictive lung disease (3%).[12]

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