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SCHIMKE IMMUNO-OSSEOUS DYSPLASIA. A CASE REPORT IN ALGERIA

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Summary

Schimke immuno -osseous dysplasia is an autosomal recessive disease, characterized by a dysmorphic syndrome associated with severe renal damage and clinical polymorphism. We report the case of a three-year - old girl hospitalized for corticosteroid-resistant nephrotic syndrome. A significant edematous syndrome, associated with a dysmorphic syndrome: bulging forehead, micrognathia, triangular face, associated with asymmetry of the two limbs, was discovered during the examination. The assessments revealed severe lymphopenia less than 800/mm3, LTCD4 and LTCD8 lymphopenia with a normal CD4/CD8 ratio and frank B lymphopenia. These elements were observed despite previously well-administered corticosteroid therapy. Schimke syndrome was selected because of the distinctive characteristics. Schimke's immuno -osseous dysplasia is a rare disease characterized by a clinical polymorphism that includes spondylo -epiphyseal dysplasia, disproportionate stature delay, characteristic facial dysmorphism and corticosteroid-resistant nephrotic syndrome, which is the usual mode of presentation of the syndrome. . The disease progresses to end-stage renal failure. Mutation of the SMARCAL1 gene, which participates in cellular DNA repair processes, explains the clinical polymorphism of this syndrome. In the presence of clinical and immunological signs; the genetic study makes it possible to confirm the diagnosis. Most patients have a life expectancy limited to early childhood or adolescence due to complications represented mainly by stroke, infections and end-stage renal disease. Schimke's immuno -osseous dysplasia is a disease characterized by clinical polymorphism and renal involvement with a guarded prognosis.

1. INTRODUCTION

Schimke's immuno -osseous dysplasia is a rare disease with an estimated incidence of 1 to 3/1,000,000 [1-5], with systemic involvement, in which several organs can be affected, notably hematopoietic, immune, skeletal and renal, characterized by its autosomal recessive transmission, monogenic caused by biallelic mutations in the

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SMARCAL1 gene (actin-dependent chromatin regulator, matrix-associated SWI/SNF2, subfamily alike 1) and a clinical polymorphism.

Spondyloepiphyseal dysplasia causing intrauterine growth retardation and stature delay from the first years of life linked to premature fusion of bone endings, associated with a dysmorphic syndrome with a low nasal bridge type, a bulbous nasal tip, short trunk and neck, lumbar lordosis, protruding abdomen, abnormal dentition, scoliosis, hyper pigmented macules , unusual hair growth [1].

Neurological manifestations include microcephaly, cognitive impairment with mild intellectual disability, migraine, and cerebrovascular manifestations such as vascular disease cerebral atherosclerosis and reversible cerebral vasoconstriction [6, 7]. These cerebrovascular damage can be aggravated by other factors such as atherosclerosis, dyslipemia and arterial hypertension which alone can lead to an alteration of the vascular wall, particularly the intima [8].

Severe forms from the first years of life through the establishment of glomerular damage often in the form of a nephrotic syndrome which rapidly progresses towards insufficiency. Terminal kidney.

Genetically, almost 50% of patients present biallelic loss-of-function mutations in the SMARCAL1 gene located on chromosome 2q35 with 18 exons, encoding an associated actin-dependent regulatory HepA -related protein (HARP). To the SWI/SNF matrix of chromatin subfamily a protein type 1. Additionally, truncating mutations have been shown to be associated with a severe phenotype, while missense mutations are associated with a less severe phenotype [5, 10].

At present, there is no specific treatment for this syndrome; management is purely symptomatic, based on regular checks with monitoring of kidney function through blood and urine tests, and thyroid function [9]. Prevention of infections can be ensured by antibiotic prophylaxis and immunoglobulin supplementation, while growth hormone treatment can be offered to correct growth retardation. Extra-renal purification is indicated in cases of end-stage renal failure; a kidney transplant may be offered on a case-by-case basis.

In this article, we report the case of a 3-year-old girl suffering from a severe form of Schimke’s immunoosseous dysplasia revealed by nephrotic syndrome.

2. DESCRIPTION OF THE CASE

3-year-old girl, hospitalized for the treatment of corticosteroid-resistant nephrotic syndrome, with a personal history of intrauterine growth retardation with a birth weight of 1800 g; a size of 43 cm and a perimeter cranium of 30 cm.

The onset dates back to 1 month before her hospitalization with the appearance of a nephrotic syndrome which required corticosteroid therapy (prednisone) for 4 weeks at a

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rate of 2 mg/kg/day and given the persistence of massive proteinuria, the patient told us was sent for further exploration and support.

Physical examination:

- Failure to thrive with a weight of 11 kg (-2.5DS) and a height of 82 cm (<-3DS),
- A significant edematous syndrome: facial puffiness, severe ascites, and edema in the external genitalia and lower limbs).
- A dysmorphic syndrome with a triangular face, bulging forehead, micrognathia with long eyelashes, associated with asymmetry of both limbs.
- High blood pressure : 149/95 mm Hg (stage 2 according to the Task Force classification)

Biological Assessments:

Biochemistry: very high proteinuria (265 mg/kg/24h) despite previously well-conducted corticosteroid therapy, Hypoalbuminemia (9 g/l), dyslipemia (Triglycerides: 2.27 g/l, Cholesterol: 3.92 g/l). Renal assessment without abnormality (urea: 0.2 g/L, blood creatinine: 4.1 mg/L).

Hemogram: hemoglobin level at 10g/l, white blood cell level at 10,000/mm3 with 8,000/mm3 neutrophils, 1,000/mm3 lymphocytes and a platelet level at 475,000elm/mm3

Immunological Assessment:

SERUM DOSAGE OF IMMUNOGLOBULINS: Pan-hypogammaglobulinemia with an IgG level 2.24g/l (7 – 11.6 g/l), IgA 0.746g/l (0.79 – 1.69 g/l) and IgM 0.387 g/l (0.4 – 0.9 g/l) L)

TB-NK lymphocyte phenotyping (Table 1): severe lymphopenia <800/mm ^{3,} with LTCD4, LTCD8 lymphopenia with a normal CD4/CD8 ratio and frank B lymphopenia.

Table 1: TB-NK Lymphocyte Phenotyping

Cells	%	Cells /mm3	Standards (Cells /mm3) (2 – 6 years)
Leukocytes	**/**	**10900**	5200 – 11000
Neutrophils	83.8%	**9137**	2300 – 6400
Eosinophils	0.1%	11	0 – 200
Monocytes	9.7%	1056	300 – 1200
Lymphocytes	6.0%	**657**	2300 – 5400
CD3+ T cells	33.7%	**221**	1400 – 3700
CD4+ T cells	34.4%	**226**	700 – 2200
CD8+ T cells	37.9%	**249**	490 – 1300
CD4+/CD8+ Ratio		**0.91**	1.5 – 2.9
CD19+ B cells	33.2%	**218**	390 – 1400
CD3-CD56+ NK cells	33.1%	218	130 – 720

Imaging

Radiology of the left wrist: bone age of 3 years.

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Telemetry of the lower limbs: asymmetry of the length of the two lower limbs with raised appearance of the left lower limb

Brain angio-MRI: hyper-intense left hemispheric cortical and ipsilateral deep thalamic lesions suggestive of acute post-ictal lesions

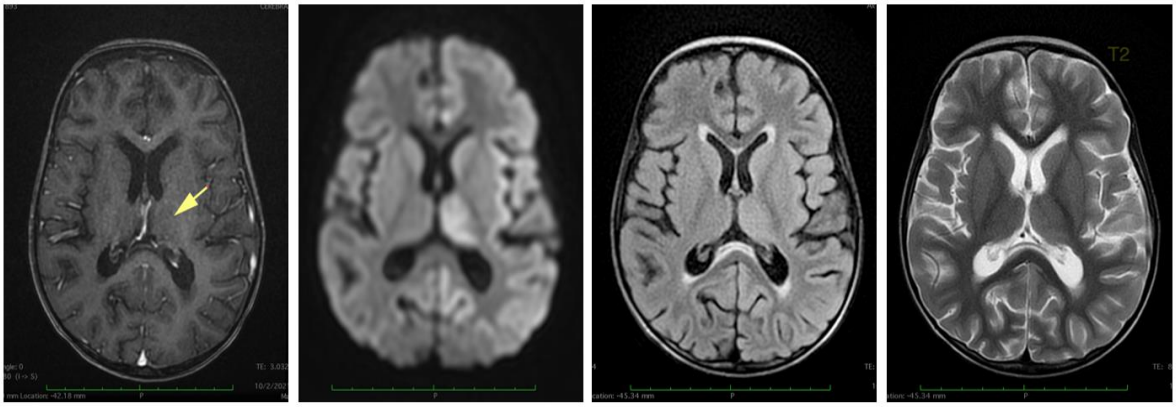

Image 1: Brain angio-MRI: left thalamic hyper intensity (Flair and T2), without perilesional edema, without significant improvement after injection and without mass effect on the midline also note a diffusion hyper signal affecting the left cuneus and the cingulate gyrus.

Renal biopsy puncture Histopathological aspects of lesions of segmental and focal hyalinosis (HSF) in its NOS variant according to the Columbia 2004 classification probably of primary nature given the clinical context which may be part of the schimkesyndrome.

Genetics: Whole exome sequencing revealed a homozygous deletion of 8 base pairs in the SMARCAL1 gene leading to the introduction of a stop codon (c.230_237 del; p.Ser77fs) confirmed by multiplex PCR. This variant has already been reported in the literature and classified as pathogenic.

Evolution: despite well-conducted corticosteroid therapy with three boluses of methyl prednisolone (500 mg/m2 of body surface area/48 hours), the girl presented renal failure with very rapid progression to the terminal stage.

3. DISCUSSION

The first description of this syndrome dates back to 1971 by Schimke , who reported the case of a 6-year-old girl who was seen for the first time in 1968 for exploration of stature delay; that after 3 years of evolution, Schimke noticed that this girl in addition to her short height below the third percentile had a dysmorphic syndrome with a shortened trunk, proximal segments of the extremities shorter than the distal segments and a waddling gait ; in addition to her mental retardation, this patient had mild enophthalmos, bilateral corneal opacities and narrow eyelid fissures. In his observation, Schimke noted the notion

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of a previous hospitalization for a serious herpes infection that required immunoglobulin infusions.

The radiological assessment showed a striking demineralization of the bones, flattened vertebral bodies, beaks in the mid-thoracic region, an increased acetabular angle, subluxation of both hips, the iliac wings had a lace-like configuration, the sella turcica was J-shaped and bone age was proportional to chronological age. Laboratory tests revealed lymphopenia less than 1000 per mm3, immunoglobulin G levels slightly decreased to 420 mg per 100 ml and 24-hour proteinuria of 1500 mg, but the striking effect was the isolated excretion of chondroitin-6-sulfate. Which made it possible to differentiate this syndrome from other types of mucopolysaccharides [2].

Since this first observation, other cases have been reported [1, 6, 9, 11, 12], the common point between these different observations is the very characteristic syndromic aspect of this pathology with very suggestive bone abnormalities associated with hemato-immunological disorders.

Advances in molecular biology have made it possible to highlight the genetic anomaly of this syndrome with the presence of mutations in the SMARCAL 1 gene which codes for the HARP protein with its highly conserved Nterminal HARP1 and HARP2 domains, which interact with the replication protein. A (RPA) binding to ssDNA. The HARP protein plays an important role in chromatin remodeling within a multiprotein complex [13, 14] and any deficiency results in increased damage associated with DNA replication and inhibition of replication in cells. , hence its essential role in the maintenance and stability of the genome [15, 16].

The HGMD professional database contains 100 mutations of the SMARCAL1 Gene dominated by missense / nonsense mutations. Truncating mutations are associated with the loss of messenger RNA; this type is the cause of severe forms of the disease, while the milder phenotypes are secondary to missense mutations [5, 17]. Our patient died from renal and cardiovascular complications (acute lung edema) linked to her severe phenotype.

4. CONCLUSION

Schimke immuno -osseous dysplasia is a rare multisystem disease characterized by spondylo -epiphyseal dysplasia, disproportionate stature delay, facial dysmorphism and corticosteroid-resistant nephrotic syndrome. Mutations in the SMARCAL1 gene explain the clinical polymorphism of the syndrome. The diagnosis is based on clinical and immunological criteria, as well as genetic study. Complications include stroke, infections and end-stage renal failure, limiting life expectancy to the early years of life or adolescence in the absence of specific effective treatment.

DECLARATION OF COMPETING INTEREST

The authors of this manuscript declared that there is no conflict of interest

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Consent for Publication

Not applicable

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