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STEROID-RESISTANT NEPHROTIC SYNDROME TYPE 14 OR SPHINGOSINE PHOSPHATE LYASE DEFICIENCY SYNDROME: A CASE REPORT IN ALGERIA

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Summary

Sphingosine-1-phosphate lyase deficiency syndrome is a rare disease, recently described, characterized by multisystem involvement including glomerulopathy, adrenal and hemato-immune. The age of onset and the course of the disease are variable; the most severe form appears very early during the neonatal period or even in-utero with rapid progression towards end-stage renal failure. We report the case of a girl, from a consanguineous marriage, followed since the age of 20 months for primary adrenal insufficiency and hypothyroidism; the etiological investigation was negative, put on hydrocortisone. At the age of 7, she presented with renal failure with stage 2 arterial hypertension. Clinical examination revealed edematous syndrome and diffuse ichthyosis. The assessments revealed nephrotic syndrome, combined immunodeficiency and non-specific multifocal segmental hyalinosis on renal biopsy. Sphingosine-1-phosphate lyase deficiency syndrome is due to an autosomal recessive mutation in the SGPL1 gene, which combines nephrotic syndrome and primary adrenal insufficiency; other disorders are often present, such as immunodeficiency, hypothyroidism and ichthyosis. Sphingosine-1-phosphate lyase deficiency syndrome is unique among sphingolipidoses presenting multiple endocrinopathies, multisystem and renal involvement. Given the multisystem and progressive nature of this rare disease, a genetic diagnosis is crucial for optimal management and appropriate screening for comorbidities in these patients.

Index Terms: Ichtyose, Glomerulopathie, Insuffisance Surrénale Primitive, Hypothyroïdie, Difficite Immunitaire.

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INTRODUCTION

Nephrotic syndrome in children is an anatomical-clinical entity, defined by a set of biological and possibly clinical signs secondary to proteinuria sufficiently abundant to cause plasma disturbances. Nephrotic syndrome in children is defined by the association of massive proteinuria greater than or equal to 50 mg/kg/24h, or greater than or equal to 40mg/m2/hour and hypoalbuminemia less than 30g/l [1 -2]**.** nephrotic syndrome is most often idiopathic, however in rare cases this disease occurs in a syndromic picture such as Galloway syndrome, Schimke syndrome [3]**.** Recently other new entities have been identified by their genetic mutations, their physiopathological mechanisms, their biochemical disorders, and by their clinical appearance. Among these new entities we find sphingosine-1-phosphate lyase deficiency syndrome, described in 2017, is a rare disease, with a very variable phenotype, from a simple form with involvement of a single organ to a severe form with an early in-uterine onset and multi-systemic involvement including endocrine, neurological, hemato-immunological and glomerulopathy with rapid progression to end-stage renal failure [4]. This disease is associated with loss-of-function mutations in SGPL1, encoding sphingosine-1-phosphate lyase which irreversibly binds to sphingosine 1-phosphate (S1P) and engages it in the final degradation step of sphingolipid metabolism [5]**.**

Clinical case

We report the case of a 7-year-old girl from a consanguineous marriage, followed since the age of 20 months for primary adrenal insufficiency and hypothyroidism; hospitalized for edematous syndrome associated with stage 2 hypertension complicated by convulsive status epilepticus secondary to a right occipital hemorrhagic stroke. Clinically, the girl had a weight of 22 kg (M), a height of 119 cm (- 0.5 SD), slight mucocutaneous pallor, generalized edema, oliguria with a diuresis of 30 mL/24 hours. and extensive ichthyosis.

The biochemical assessment made it possible to make the diagnosis of nephrotic syndrome with 24-hour proteinuria of 150 mg/kg/24 hours and hypoalbuminemia of 16 g/L, associated with renal failure with blood creatinine of 102 mg/L (901, 7 µmol/l) and a blood urea level of 2 g/L (33.2 mmol/l), serum calcium of 82 mg/L, serum sodium of 136 mEq/L and serum potassium of 4.1 mEq/L. The hemato-immunological assessment: revealed a combined immunodeficiency with Hypo-IgG and IgA, profound Pan-T, B and NK lymphopenia and a clear reduction in naive CD4+ T lymphocytes (Table 1-3)

Table 1: Serum Dosage of Immunoglobulins and Complement Fractions (Technique: laser nephelometry (IgG, IgA, IgM, IgD, C3, C4, C1Inh), chemiluminescence (total IgE)

Immunoglobulin	Concentration	Normal values (6 – 9 years)
IgG	**3.2 g/l**	6.9 – 11.5 **g/l**
IgA	**0.47 g/l**	0.68 – 1.94 **g/l**
IgM	0.42 **g/l**	0.39 – 0.79 **g/l**

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Table 2: TB-NK lymphocyte phenotyping

Cells	%	Cells /mm ^{3}	Standards (Cells/mm ^{3}) (6 – 12 years)
Leukocytes	**100%**	**5320**	4400 – 9500
Neutrophils	100.8%	5363	2600 – 6300
Eosinophils	0.5%	**24**	0 – 200
Monocytes	0.6%	**33**	300 – 900
Lymphocytes	1.0%	**54**	1900 – 3700
CD3+ T cells	65.4%	**36**	1200 – 2600
CD4+ T cells	25.6%	**14**	650 – 1500
CD8+ T cells	34.4%	**19**	370 – 1100
CD4+/CD8+ Ratio		**0.74**	1.5 – 2.9
CD19+ B cells	29.8%	**16**	270 – 860
CD3-CD56+ NK cells	4.8%	**3**	100 – 480

Table 3: Extended immunophenotyping of T lymphocytes

T lymphocyte	%	Standards (%) (6 – 12 years old)
$CD4^+CD45RA^+$ T cells /$CD4^+$ T cells%	**13.69**	53 – 86
$CD4^+CD45RO^+$ T cells /$CD4^+$ T cells%	86.31	/
$CD8^+CD45RA^+$ T cells /$CD8^+$ T cells%	**66.14**	69 – 97
$CD8^+CD45RO^+$ T cells /$CD8^+$ T cells%	33.86	/
$CD4^+_{RTE}CD45RA^+CD31^+$ T cells /$CD4^+$ T cells% (F)	4.35	25.8 – 68
$CD4_{CM}CD45RA^-CCR7^+$ T cells/$CD4^+$ T cells%	**1.66**	12.2-26.2
$CD4_{Naive}CD45RA^+CCR7^+$ T cells/$CD4^+$ T cells%	**0.28**	15.5-59.4
$CD4_{EM}CD45RA^-CCR7^-$ T cells/$CD4^+$ T cells%	**86.43**	10.6-34.2
$CD4_{TEMRA}CD45RA^+CCR7^-$ T cells/$CD4^+$ T cells%	11.63	4.5-43.6
$CD8_{CM}CD45RA^-CCR7^+$ T cells/$CD8^+$ T cells%	14.65	1.2-3.8
$CD8_{Naive}CD45RA^+CCR7^+$ T cells/$CD8^+$ T cells%	17.74	5.5-39.7
$CD8_{EM}CD45RA^-CCR7^-$ T cells/$CD8^+$ T cells%	23.91	20.1-44.7
$CD8_{TEMRA}CD45RA^+CCR7^-$ T cells/$CD8^+$ T cells%	43.7	21.5-61

Pathological study revealed focal segmental hyalinosis. For the genetic study, exome sequencing revealed a mutation in the SGPL1 gene coding for the enzyme Sphingosine-1-Phosphate Lyase 1. This is an insertion of a PB at position 261 of the exon 6 (NM_003901.4: c.261+1G>A) leading to aberrant transcription consequently to the total absence of the enzyme. Evolution, the patient presented during the second week of hospitalization with staphylococcus epidermis septecism having progressed well under antibiotic treatment and substitution with multivalent immunoglobolins, however on the nephrological level there was a rapid deterioration of renal function with a progression towards end-stage renal failure after a few weeks with indication of extra-renal purification.

DISCUSSION

The main functional characteristics of sphingosine phosphate lyase (SPL) were first described by Stoffel et al in 1969. Indeed, SPL is an enzyme involved in the degradation of sphingolipids to produce a long-chain aldehyde and phosphate. ethanolamine (EP) [6]; its inactivation leads to an accumulation of sphingolipid intermediates which will be the cause of an overload with cellular dysfunction or even cellular apoptosis. And it was only

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in 2017 that recessive mutations in the human SPL gene SGPL1 were identified as the cause of a new inborn error of metabolism associated with multiorgan damage, mainly renal, endocrine, neurology and immune [7-12]. Currently this syndrome must be considered in the face of a syndromic association of certain clinical signs (table 4), which requires biological exploration, imaging and the search for a genetic mutation.

Table 4: The clinical signs, biochemical results and imaging signs most frequently encountered in sphingosine phosphate lyase deficiency syndrome [4,13-15]

Clinical signs - Skin damage	Ichthyosis Acanthosis, hyperpigmentation
- Kidney damage	Corticosteroid-resistant nephrotic syndrome.
- Endocrine damage	Primary adrenal insufficiency Primary hypothyroidism Testicular failure
- Neurological damage	Psychomotor delay or regression Cranial nerve damage Sensorineural hearing loss Peripheral neuropathy
Immunological damage	Seizures B and T lymphopenia Hypogammaglobulinemia
Biochemical analyzes Plasma metabolism	Increased sphingosine-1-phosphate and/or other sphingolipids An increase in the plasma sphingosine/dihydrosphingosine ratio
Imaging - Brain MRI	Damage to the corpus callosum (agenesis or dysgenesis) Dark gray nuclei Microcephaly Cortical atrophy Cerebellar hypoplasia Renal hypertrophy
- Abdominal ultrasound	Enlarged adrenal glands Calcifications of the adrenal glandst

The transmission of this syndrome is autosomal recessive, molecular genetic tests by exome sequencing have made it possible to identify a mutation in the SGPL1 gene coding for the enzyme Sphingosine-1-Phosphate Lyase 1. This is an insertion of a PB in position 261 of exon 6 (NM_003901.4: c.261+1G>A) leading to aberrant transcription and consequently the total absence of the enzyme [8]. However, it should be noted that there is no genotype-phenotype correlation, with variability even within families, because the symptoms can be in-utero or at a more advanced age within the same family [4,7], this

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intrafamilial variability can be explained by the presence of other genetic factors such as SGPP1, SGPP2, SPHK1, SPHK2, SPNS2 or S1PR1-5 involved in S1P metabolism and signaling. In the absence of a specific treatment, the management of patients with this syndrome is purely symptomatic, this management is based on the treatment of different disorders with a location of glucocorticoids and mineralocorticoids associated or not with sodium supplementation. With appropriate advice for the management of emergency situations, replacement with thyroxine for hypothyroidism and medical management based on supplementation with calcium, alfa, iron and erythropoietin for insufficiency kidney or even a kidney transplant. With regard to the immune deficiency, rigorous monitoring of lymphocyte levels with therapeutic measures against all infections whatever their nature through early appropriate antibiotic therapy and immunoglobulin infusions [4].

In the context of therapeutic perspective, new therapies are being evaluated such as bone marrow transplantation, gene therapy and enzyme substitution by the administration of soluble SPL, which have had positive effects in a preclinical model and which are considered a promising avenue

CONCLUSION

Steroid-resistant nephrotic syndrome type 14 or Sphingosine phosphate lyase deficiency syndrome is a rare multisystem disease characterized by glomerular involvement, endocrine with adrenal and thyroid insufficiency, neurology and immunodeficiency. Mutations in the SGPL1 gene explain the clinical polymorphism of the syndrome. The diagnosis is based on clinical and immunological criteria, as well as a genetic study. Complications include serious endocrine disorders, infections and end-stage renal failure, limiting life expectancy to the early years of life or adolescence in the absence of effective specific treatment [16,17].

Declaration of Competing Interest

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

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