4-YEARS-OLD GIRL WITH SPLENOMEGALY AND INTERMITENT THROMBOPENIA WITH MORE THAN TWO YEARS OF EVOLUTION

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CASE REPORT

We described a case of a 4-years-old girl who has splenomegaly, intermittent thrombopenia, dysmetria, minimal ataxia, failure to thrive and vertical supranuclear gaze onset.

Table 1. Blood count results.

Magnitude	Result	Reference interval
Erythrocytes	4.8 x10^{12}/L	3.9-5.3
Hemoglobin	12 g/dL	11.5-13.5
Hematocrit	35.8 %	34-40
MCV	76 fL	75-87
MCH	25.5 pg	25-35
MCHC	35 g/dL	30.4-36.5
RDW	14 %	11.5-18
Platelets	**76 x10^{9}/L***	150-500
Plateletcrit	**0.05 %***	0.1-0.4
Leukocytes	**4.7 x10^{9}/L***	5-11.9

*Results outside the reference interval. MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RDW: red cell distribution width.

Given this clinical picture, the analysis of oxysterols, lysosphingolipids and chitotriosidase in plasma was requested. A mild elevation of cholestane-3β,5α,6β-triol concentration: 30 ng/mL, reference values (R.V.)=0.5-8, and, an important increase of lysosphingomyelin-509 (lysoSM-509) levels: 15,548 nmol/L, R.V.=<3500, were detected. These results together with the normal values of the rest of lysosphingolipids analyzed [glucosylsphingosine, lysoshingomyelin, lysoglobotriaosylsphingosine, lyso-monosialoganglioside GM1, lyso-monosialoganglioside GM2], and normality of the chitotriosidase activity directed the diagnosis to Niemann-Pick type C (NPC) disease.

Table 2. Results of targeted metabolic study in plasma.

Magnitude	Result	Reference interval
Chitotriosidase	70 nmol/h/mL	17-211
3β,5α,6β-colestanotriol	**30 ng/mL***	0.5-8
LisoGb1	0.5 nmol/L	<1,4
LisoGb3	Undetectable	<2.3
LisoSM	51.3 nmol/L	<60
LisoSM-509	**15,548 nmol/L***	<3,530
LisoGM1	Undetectable	Undetectable
LisoGM2	Undetectable	<0.2

Exome study was carried out and two mutations (c.[2324A>C]+[1955C>T]) were detected in heterocygosis in *NPC1* gene. Moreover, a mutation in heterocygosis was also detected in *SMPD1* gene (c.[908_910delGCC] + [=]), so sphingomyelinase activity was analyzed, being normal. Patient started treatment with miglustat.

NPC is a lysosomal storage disease resulting from the deficiency of NPC1 or NPC2 proteins involved in the lysosomal cholesterol transport. This blockage leads to an accumulation of intra-lysosomal cholesterol and other complex lipids resulting in a progressive neurological degeneration and organ dysfunction[4]. Niemann-Pick type A/B (NPAB) disease is produced by a sphingomyelinase deficiency, leading to an accumulation of sphingomyelin and other lipids secondarily[5].

In the presence of hepatosplenomegaly and hematological alterations, lysosomal diseases should be included in the differential diagnosis, since these clinical manifestations are frequent in this group of diseases, mainly in NPC, NPAB and Gaucher disease. Targeted analysis of oxysterols, lyso-sphingolipids and chitotriosidase activity is very useful in the differential diagnosis between the three entities.

The case reported here represents a curious case affected of NPC and carrier of NPAB disease in whose the initial evaluation of plasma oxysterols and lysosphingolipids oriented to the correct diagnosis amongst different entities that share common clinical manifestations, before the genetic study results.

METHODS

The analysis of lysosphingolipids and oxysterols was performed by ultra-performance liquid chromatography-tandem mass spectrometry (ACQUITY-Xevo TQ-XS, Waters Corporation) as described by Polo et al. [1,2] and Pajares et al. [3] respectively. Plasma chitotriosidase was determined using the fluorescent substrate 4-methylumbelliferyl β-D-N,N′,N″-triacetylchitotrioside. Plasma sample (10 µL) was incubated with 100 µL of substrate solution for 1 hour at 37 °C in opaque 96-well plate. The reaction was stopped by adding 150 µL of carbonate-bicarbonate buffer (0.5 M pH 10.7) to each well. Fluorescence intensity was measured at an emission wavelength of 460 nm and an excitation wavelength of 360 nm, on a PolarStar Omega instrument (BMG Labtech).

References

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