NIEMANN-PICK DISEASE - TYPE B - ONE CENTER EXPERIENCE

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ABSTRACT

Niemann-Pick disease (NPD) is an autosomal recessive lipid storage disorder that results from the deficiency of a lysosomal enzyme, acid sphingomyelinase. It is subdivided into acute, lethal neuronopathic type A and chronic visceral type B, explained by the different residual activity levels of the enzyme. For 5 years (2002-2007) the diagnosis NPD was proved in 5 children (4 boys and one girl of gypsy ancestry; unrelated) by clinical and laboratory findings and positive mutational analysis. All children have been with normal appearance at birth. In four of them clinical manifestation has started up to 3 years of age, in one - at 7 years, with enlargement of liver and spleen. Symptoms of hepatic injury were: fatigue (4/5), abdominal pain (3/5), oedema (2/5), hepatomegaly (5/5), severe splenomegaly (5/5), elevated aminotransferases (4/5), pancytopenia (3/5), elevated cholesterol (5/5). Cherry-red spot found in 2/5. Myelogram with foamy cells - 4/5. Specific laboratory test: decreased sphingomyelinase activity 5/5. Mutational analysis - all patients were found homozygotes for a specific mutation (W391G), typical for patients of gypsy origin.

Key words: Niemann-Pick disease, NPD, DNA analysis

INTRODUCTION

Acid sphingomyelinase deficiencies are heterogeneous, autosomal recessive lysosomal disorders characterized by an accumulation of undegraded sphingomyelin and other lipids in the lysosomes of multiple cell types, particularly those of macrophage/monocyte lineage and in ganglion cells in the central nervous system. The exact biochemical basis of the different types has not been completely clarified. However, tissue-specific sphingomyelinase deficiency, sphingomyelinase isoenzyme deficiencies, or a sphingomyelinase activator protein deficiency also may be involved. Lipid-filled "foam cells" may be noted in the bone marrow, liver, spleen, adrenals, brain, lymph nodes, and lungs. "Sea-blue histiocytes" may also be demonstrated with Romanovsky staining. Deficient activity of sphingomyelinase may be demonstrated in leucocytes or cultured skin fibroblasts. Traditional classifications subdivide NPD phenotypes into type A (OMIM 257200), a lethal neurodegenerative condition with early onset and death in the first 2-3 years of life, and chronic visceral type B (OMIM 607616) with variable severity and compatible with survival into adulthood. ASMase is encoded by the sphingomyelinase gene (SMPD1) on chromosome 11 (11p15.1-p15.4). The complete sphingomyelinase genomic

region has been isolated and sequenced. More than 50 mutations that cause NPD types A and B have been identified, namely, single-base substitutions and small deletions.

Niemann-Pick types A (NPA) and B (NPB) are phenotypes within a continuum of disease that vary by age of onset, absence or presence of neurologic disease, severity of features, and survival. Visceral features may include growth retardation; hepatomegaly, often without liver dysfunction; splenomegaly; gastrointestinal disturbances; hyperlipidemia; pulmonary disease; osteoporosis; lymphadenopathy; pancytopenia; and ocular abnormalities, particularly cherry-red maculae. NPA and NPB are rare disorders that occur in all races (a combined frequency of 1 in 248,000 in Australia. Niemann-Pick type A, the more severe phenotype, displays progressive neurovisceral disease within the first several months of life. Survival depends on supportive care but usually does not extend beyond age 2-3 years. Prolonged neonatal jaundice; hepatosplenomegaly, usually without liver dysfunction; and failure to thrive are among the earliest features. Affected individuals experience progressive hypotonia, muscle weakness, intellectual decline, and loss of milestones that transforms to spasticity and rigidity at the end stages of the disease. NPA is particularly prevalent in the Ashkenazi Jewish population, in which about 1 in 80 persons are carriers. Niemann-Pick type B is a heterogeneous, nonneuronopathic disease with visceral features as described above. The disease is frequently diagnosed in childhood to adolescence, with survival into adulthood. Hepatosplenomegaly is most preva-

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lent during childhood but tends to become less conspicuous with age. Within a subpopulation of patients with this subtype of disease, pulmonary disease is a significant source of morbidity. The disease is pan-ethnic in nature, with highest incidence in individuals of Turkish, Arabic, and North African descent and less frequency among those of Ashkenazi Jewish heritage. Intermediate variants of acid sphingomyelinase deficiency are common and comprise 64% of affected individuals in central Europe. These intermediate variants are defined by a cluster of visceral features and a protracted neuropathic course.

MATERIAL AND METHODS

For 5 years (2002-2007) the diagnosis Niemann-Pick disease, type B was proved in 5 children from North-Eastern Bulgaria (4 boys and one girl, 3-16 years, median age of 5.3 years). Pedigree analysis was performed to evaluate the familial data, the origin and ethnicity. All patients are unrelated and are the only affected family member; all have Gypsy ancestry. The diagnosis was based on detailed clinical examination and biochemical findings. Enzyme assays, performed at the National Genetic Laboratory - Sofia, included AMSase activity in peripheral blood white cells or in cultured skin fibroblasts (in one patient) and/or chitotriosidase in plasma. DNA analysis of SMPD1 gene was performed in all patients.

RESULTS

All patients are of gypsy origin and come from 5 unrelated gypsy families (sporadic cases, which is consistent with AR inheritance). Consanguinity is denied. For this ethnic minority in Bulgaria is typical to mate within the group, so AR disorders are more common, than compared to the whole population. Families come from North-Eastern part of the country. The signs and symptoms of visceral involvement were similar to those described previously in studies of NPD type B patients. The individual data are summarized in table 1. Children have been with normal appearance at birth. Onset of the disease was within the first 2 years of life in all cases; however the diagnosis was established in 4 patients up to age of 3 years; in one the diagnosis was delayed until age 7 years. Initial clinical manifestations included hepatosplenomegaly (invariably present at the first examination), recurrent respiratory infections and delayed developmental milestones (fig.1). Till their referral to a specialist (children's gastroenterologist) the usual clinical diagnosis has been chronic hepatitis, liver cirrhosis, portal hypertension. Widen clinical thinking brought into consideration possible metabolic disease. For that reason evaluation of chito-triosidase in plasma was performed and the elevated levels pointed the diagnosis sphingolipidosis. At the most recent examination, low stature was common: all patients were below the 3rd percentile of the reference

values. Hepatosplenomegaly with massive enlargement of the organs was present in all children. Serum aminotransferase activity (AST and ALT) was increased in

Fig. 1 A NPD patient - low stature, hepatosplenomegaly

4/5 cases.

The patients reported recurrent chest infections. Lung infiltration and other pulmonary changes were not found.

Ocular features - macular halo, were found in 2 children, in the rest the fundoscopy was unremarkable.

Two of the patients had intellectual deficit, one of which with profound disability (severely impaired verbal and nonverbal communication, fully dependent behavior).

Molecular analysis of SMPD1 gene found a specific mutation (W391G), characteristic for the gypsy population on the Balkan Peninsula, first identified in a Serbian patient with gypsy origin. All patients showed homozygous status for the W391G mutation.

CONCLUSION

NPD is difficult to diagnose because of the variable clinical manifestation and rarity of the disease. In children with unclear hepatic and spleen involvement NPD should be considered and specific lab tests and mutation analysis should be performed.

Table 1. Clinical data in NPD patients homozygous for the W391G mutation

Pt No	Sex	Age at onset (years)	Age at examination (years)	Sphingo-myelinase activity	Chitotriosidase in plasma ^a	Clinical findings at most recent examination							MR
						Low stature	Hepato-megaly	Spleno-megaly	Serum AST/ALT	Foam cells in bone marrow	Pulmonary infiltration	Cherry red spot	
1.	M	<1	16	ND	671	+	13	+	55/63	+	-	+	+
2.	M	<3	14	4 ^L 26 ^F	182	+	18	18	N/N	+	-	+	-
3.	M	<1	1	ND	614	+	14	14	80/44	+	-	-	-
4.	M	<7	14	ND	9048	+	4	17	50/59	+	ND	ND	+

ND - no data

^L - Sphingo-myelinase activity measured in leucocytes; reference range 24-135 nmol/17h/mg protein (N=36)

^F - Sphingo-myelinase activity measured in fibroblasts; reference range 102- 590 nmol/h/mg protein (N=86)

^a - Reference range 34±

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