The Natural History of Type B Niemann-Pick Disease: Results From a 10-Year Longitudinal Study

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ABSTRACT. Objectives. Type B Niemann-Pick disease (NPD-B) caused by acid sphingomyelinase deficiency is a rare, autosomal recessive, lysosomal storage disorder with a broad range of disease severity. The objectives of this study were to document the natural history of the disease in a large, clinically heterogeneous patient population that was followed for a period of 10 years and to determine how genotype influences phenotype.

Methods. Twenty-nine patients with NPD-B had serial evaluations at least 9 months apart. Organ volumes, hematologic indices, lipid concentrations, pulmonary function, and hepatic activity were studied, and individual phenotypic severity was compared with genotype.

Results. All patients with intact spleens had splenomegaly (mean volume: 12.7 multiples of normal [MN]; range: 4.5–27.3 MN), and all but 1 had hepatomegaly (mean value: 12.7 multiples of normal [MN]; range: 0.93–3.21 MN). At initial visit, 39% had thrombocytopenia and 3% had leukopenia (mean volume: 1.91 MN; range: 0.93–3.21 MN). At initial visit, the percentages increased to 54% and 34%, respectively. Mean annual decreases in platelet count and leukocyte count were 7 × 10⁹ and 0.2 × 10⁹ per mm³, respectively. The typical atherogenic lipid profile was worse in older patients. A total of 69% of patients had low diffusion capacity for carbon monoxide, and more than one third had low forced expiratory volume in 1 second, forced vital capacity, and forced expiratory volume in 1 second/forced vital capacity at initial visit. All measurements of pulmonary function showed a gradual deterioration over time. Liver dysfunction was characterized by stable elevation of hepatic transaminases and bilirubin. Homozygotes for ΔR608, P323A, and P330R had milder disease than patients with other genotypes.


Niemann-Pick disease (NPD) is a lysosomal storage disease caused by deficient activity of acid sphingomyelinase (ASM; sphingomyelin phosphodiesterase; EC 3.1.4.12) and the accumulation of sphingomyelin within cells of the monocyte-macrophage system. Types A and B NPD are inherited as autosomal recessive traits and result from allelic mutations in the ASM gene. Type A disease (NPD-A), which has an Ashkenazi Jewish predilection, is a fatal neurodegenerative disorder of infancy. In contrast, type B NPD (NPD-B), which is panethnic, is a nonneuronopathic disease characterized by hepatosplenomegaly, hyperlipidemia, and pulmonary involvement, with most patients living into adulthood. Other, more variable features of NPD-B may include liver dysfunction, cardiac disease, retinal stigmata, and growth retardation.

There is a broad spectrum of disease manifestations among NPD-B patients, ranging from onset in childhood with massive organomegaly, secondary hypersplenism, growth restriction, and later pulmonary involvement or liver failure to a milder, attenuated course. As in other lysosomal storage diseases, this marked phenotypic variability is influenced by genotype, although other factors such as gender and age may also contribute to disease severity. To date, the phenotypic variability and the delineation of genotype/phenotype correlations have been limited to single case descriptions or reports of small series of patients, rather than detailed longitudinal studies. This lack of information about the natural history of NPD-B makes it difficult not only to provide prognostic information to patients and families but also to evaluate potential therapeutic interventions, such as enzyme replacement therapy.

We now report the results of a 10-year longitudinal study of the phenotypic heterogeneity of NPD-B. In addition, we describe the natural history of NPD-B–related hematologic disease, hyperlipidemia, pulmonary involvement, and liver dysfunction and compare disease progression with age, gender, and genotype.
METHODS

Study Patients

Twenty-nine patients with NPD-B (15 male, 14 female; age range at entry: 2.2–64.1 years) from 23 unrelated families were evaluated. At entry, 22 patients were in the pediatric age group (<18 years old) and 9 were adults (>18 years old). Two patients had undergone splenectomy before entry into the study, and 1 had undergone a bone marrow transplantation but had lost the graft and continued to display disease manifestations. One patient was started on statin therapy at age 29. One splenectomized patient required oxygen at 61 years of age, and a nonsplenectomized patient required oxygen at night starting at 11 years of age. Of the 23 families, 20 were of mixed European/white descent, 1 was of Yemeni descent, and 2 were Ashkenazi Jewish.

Each patient had ≥2 visits to the Mount Sinai General Clinical Research Center at least 9 months apart (mean number of visits: 4.3; range: 2–13) between 1992 and 2002. The length of time from initial to final visit ranged from 1 to 10 years (mean: 4.3 years). The study was approved by the Mount Sinai School of Medicine Institutional Review Board. Voluntary, written informed consent was obtained from each patient or guardian, and minor assent was obtained from children who were >6 years old before any study-related procedures. The diagnosis of NPD-B was confirmed in each patient by the demonstration of reduced ASM activity in isolated leukocytes and/or cultured skin fibroblasts and by the identification of 2 disease-causing ASM mutations.

Clinical Studies

Medical histories and physical examinations were performed at each visit. The standard deviation and z score for the most recent height and weight were determined using the Epi Info 2000 Program (Version 1.1.2, Centers for Disease Control and Prevention, Atlanta, GA, www.cdc.gov/epiinfo/ei2000.htm; data not shown). The diagnosis of NPD-B was confirmed in each patient by the reduction of normal ASM activity in isolated leukocytes and/or cultured skin fibroblasts and by the identification of 2 disease-causing ASM mutations.

Determination of Genotype

Dot-blot hybridization using allele-specific oligonucleotides was used to screen for the previously identified common mutations in the ASM gene (R496L, L302P, fs530, and ΔR608). In patients with unidentified mutations, sequencing of the entire ASM gene was performed as previously described. Putative mutations were confirmed by dot-blot hybridization or endonuclease digestion of polymerase chain reaction–amplified genomic DNA from the proband and family members.

Determination of Phenotypic Severity Score and Genotype/Phenotype Correlations

To evaluate the relationship between phenotype and genotype, we assigned phenotypic severity scores. Spleen and liver size, platelet count, high-density lipoprotein (HDL) cholesterol concentration, pediatric growth restriction, and adult pulmonary disease were used to determine overall phenotypic severity. Scores were given for each variable, ranging from mild (score = 1: spleen volume 1–5 multiples of normal [MN]; liver volume 1–1.25 MN; platelet count >150 × 10^9 per mm^3; HDL cholesterol >35 mg/dL) to severe (score = 4: spleen volume >15.1 MN; liver volume >1.76 MN; platelet count <49 × 10^9 per mm^3; HDL cholesterol <14 mg/dL). For patients who were <18 years old, growth restriction was graded from 1 (mild: height z score between 0 and −1) to 3 (severe: height z score <−2.1). Patients who were >18 years old and did not have pulmonary signs were given a score of 1, those with cyanosis or clubbing were given a score of 2, and those with oxygen dependence were given a score of 3. The sum of the scores from each category was the overall phenotypic severity score, which was categorized as mild (overall score 6–11), moderate (overall score 12–14) or severe (overall score ≥15).

Statistical Analysis

To evaluate the initial value for hematologic indices, lipid profile, lung function, and lipids, we used multiple regression (or equivalently 2-way analysis of variance) with variables age group (<18 or >18) and gender. This allowed us to give mean values for age group adjusted by gender and the reverse.

The definitive analysis of changes over time was performed by fitting a straight line to each patient’s data using a random intercept model using PROC MIXED of SAS. (We also tried random slope and intercept model and other variants but on the basis of these results found no evidence that these more complicated models were helpful.) This analysis allows for arbitrary number of observations per patient over time. The method gives an estimate of the annual change, which gives more weight to patients with a longer follow-up and many visits than to patients with a shorter follow-up and few visits. In addition, we compared the percentage of final and initial values that were outside the normal range using McNemar test.

RESULTS

Hepatosplenomegaly and Hematologic Indices

Spleen volumes ranged from 4.5 to 27.3 MN, with a mean of 12.7 MN. The mean liver volume was 1.91 MN (range: 0.93–3.21 MN). Two patients who had undergone splenectomy were excluded from the analyses of the hematologic values, because the abnormalities arise from hypersplenism.

The adjusted mean leukocyte count and hemoglobin concentration were lower in patients who were <18 years old, whereas the adjusted mean platelet count was lower in patients who were >18 years old (Fig 1). No significant gender disparities were found for the hematologic indices. At the final visit, significantly more patients had abnormal values for leukocyte count and platelet count (34% and 54%, respectively) than at the initial visit (3% and 39%, respectively; Table 1). Analagously, mean annual

![Fig 1](https://www.pediatrics.org/cgi/doi/10.1542/peds.2004-0887)
rates of change for leukocytes and platelet counts were \(-0.19 \times 10^3\) per mm\(^3\) \((P = .001)\) and \(-6.84 \times 10^3\) per mm\(^3\) \((P < .001)\), respectively, predicting a gradual worsening over time for both. Figure 2 shows the gradual decline in these indices in a patient who had a severe phenotype and was followed for the longest time.

**Lipid Abnormalities**

Most patients had borderline to high total and low-density lipoprotein (LDL) cholesterol, low HDL cholesterol, and borderline to high triglycerides at the initial visit (Table 1), with the adults having worse initial values than children (Fig 1). Male patients had higher triglycerides and lower HDL cholesterol than female patients at the first visit (triglycerides: 336.1 mg/dL vs 229.6 mg/dL, \(P = .04\); HDL cholesterol: 14.3 mg/dL vs 24.7 mg/dL, \(P = .047\)). Evaluation of the estimated annual change showed statistically significant improvement for HDL and triglycerides with yearly changes of 0.47 mg/dL \((P = .004)\) and \(-7.37\) mg/dL \((P < .001)\), respectively.

![Fig 2. Change in hematologic indices for the patient who was followed for the longest period.](image)
respondingly, the percentage of patients with values outside the normal range declined significantly for triglycerides, with a change from 83% abnormal at baseline to 68% abnormal at last visit ($P < .05$). In contrast, the percentage of patients with abnormal values did not change for HDL cholesterol. The improvement in total cholesterol was of borderline significance on the basis of estimated annual change. The results were inconclusive for LDL, with the most sensitive statistical method showing a small, nonsignificant improvement and the generally cruder analysis examining percentage with abnormal readings showing a significant deterioration.

**Pulmonary Studies**

More than one third of patients had abnormal forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC values on entry into the study (Table 1). In addition, more than two thirds of the patients had a low DLCO at the initial visit. At the initial visit, mean values for FEV1, FVC, FEV1/FVC, DLCO, and total lung capacity (TLC) were higher in patients who were <18 years old and lower in patients who were >18 years old (Fig 1). These differences for the last 3 outcomes were statistically significant for FEV1/FVC, DLCO, and TLC. For FEV1/FVC, DLCO, and TLC, the respective $P$ values were .001, .02, and .004. Estimated mean annual changes were negative for all measures of pulmonary function (Table 1), and this deterioration was statistically significant for FEV1 ($P = .014$) and FEV1/FVC ($P < .001$) with estimated annual mean changes of $-1.6\%$ predicted and $-0.7\%$ predicted, respectively.

**Liver Function**

At the initial visit, there were no significant differences in liver function with respect to gender or age (Fig 1), with the exception of total bilirubin, which was higher in patients who were >18 years old ($P = .01$). Similarly, no statistically significant changes in liver function, whether viewed on the basis of mean change over time or of percentage of patients with abnormalities, were noted (Table 1). Both transaminases tended to remain elevated in most patients throughout the study. All patients had normal bilirubin values throughout the study. One patient developed hepatic dysfunction ~2 years after his last visit and subsequently died of liver failure.

**Genotype–Phenotype Correlations**

The 29 patients in the study had 22 different genotypes (Table 2). Eight patients had a mild phenotype, 11 had a moderate phenotype, and 10 had a severe phenotype. The genotypes that were associated with those phenotypic severity categories are shown in Table 2. As has been previously reported, individuals who were homozygous for ΔR608 had a milder disease phenotype. In addition, patients who were homozygous for P323A and P330R had less severe disease than patients with all other genotypes.

### Mortality Among Study Patients

One patient died of liver failure in his early 10s, another died of a traumatic subdural hematoma at 9 years of age, and a third died at 18 years from long-term complications after a failed bone marrow transplant.

**DISCUSSION**

The results of this study provide the first data on the natural history of the disease manifestations in NPD-B. The NPD-B phenotype, which displays a broad range of phenotypic severity, included hepatosplenomegaly with secondary hypersplenism, an atherogenic lipid profile, abnormal pulmonary function, and mild liver dysfunction.

The natural history of the hematologic complications was characterized by decreasing leukocyte and platelet counts with age, whereas the hemoglobin concentration remained stable. Presumably, the decreasing cell counts result from progressive hypersplenism. The clinical consequences of the progressive leukopenia and thrombocytopenia of particular importance to NPD-B patients include infection, particularly of the respiratory tract, and bleeding episodes, respectively.

The majority of patients studied had an atherogenic lipid profile characterized by low HDL cholesterol, high total and LDL cholesterol, and high triglycerides. The finding that HDL cholesterol is decreased at all ages is concerning because this is a major risk factor for coronary artery disease and studies are continuing to assess the clinical consequences of this profile. Although the total cholesterol, LDL cholesterol, and triglycerides may be amenable to dietary modifications and exercise, these interventions may not be possible in more severely affected NPD-B patients because of growth restriction and pulmonary disease, and transaminases have

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**TABLE 2.** Classification of Genotypes Based on Phenotypic Severity as Determined by Cumulative Phenotypic Severity Score

<table>
<thead>
<tr>
<th>Phenotypic Severity</th>
<th>Mutation 1</th>
<th>Mutation 2</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>ΔR608</td>
<td>ΔR608</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>P223A</td>
<td>P323A</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>P330R</td>
<td>P330R</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>G245S</td>
<td>R474W</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>A196P</td>
<td>R376H</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>R496C</td>
<td>W397F</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>R496C</td>
<td>W397F</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>A196P</td>
<td>C157R</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>A196P</td>
<td>C431R</td>
<td>1</td>
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<td>R600H</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>R228C</td>
<td>R228C</td>
<td>1</td>
</tr>
</tbody>
</table>

* A common NPD-A mutation.
been noted to increase markedly in some affected patients after administration of statins (M.M.M., unpublished observations), which thus might be contraindicated. Therefore, the treatment of the lipid abnormalities in NPD-B is problematic.

The pulmonary function tests revealed a restrictive pattern of lung involvement with abnormal diffusing capacity, compatible with interstitial lung disease. The progressive nature of the pulmonary involvement is supported by the consistent findings that (1) older patients have lower mean PFT values than younger patients, (2) the number of patients with abnormal PFT values increased with time, and (3) the calculated mean annual change was negative for all measures of pulmonary function. Although many NPD-B patients are asymptomatic, more severely affected patients may exhibit cough, shortness of breath, and recurrent respiratory infections. Cytosis, clubbing, rales, and rhonchi may be present on physical examination in such patients. The typical chest radiograph has interstitial infiltrates with reticuloendothelial changes and areas of ground glass density, often out of proportion to clinical manifestations. Studies in ASM knockout mice, which have histopathologic and clinical changes similar to human NPD-B patients, reveal that inflammation, abnormal surfactant catabolism, and abnormal surfactant composition all contribute to lung abnormalities. However, more detailed studies of lung function are required to understand better the pathophysiology of the pulmonary disease in NPD-B.

The evaluation of liver function revealed mild elevations of serum transaminase activities and bilirubin concentrations. Although none of the patients whom we studied underwent liver biopsy as part of the clinical protocol, several had had biopsies before entry to the study. In these patients and in other reports form the literature, biopsy specimens show vacuolated, lipid-laden cells with or without fibrosis. In addition, several cases of severe liver disease have been reported in patients with NPD-B, ranging from children with fatal hepatic failure to adults with cirrhosis and portal hypertension. These clinical descriptions, coupled with the findings on pathologic examination of the liver, raise concerns about the ultimate contribution of liver dysfunction to the morbidity and mortality of NPD-B patients. Serum transaminases were abnormal in most patients and tended not to change significantly over time. Our results raise the question of whether these measurements of liver function are adequate to assess the full range of liver disease in patients with NPD-B. Physical stigmata and radiographic findings may be more helpful in ascertaining the extent and ultimate prognosis of the liver involvement.

Many ASM mutations have been identified in unrelated NPD-B patients, and a single common mutation, ΔR608, has been described. Because of the number of private mutations and the rarity of this disease, a phenotypic severity score was used to correlate phenotype with genotype. Mild disease was associated with homozygosity for missense mutations such as ΔR608, P323A, and P330R. Patients who were compound heterozygotes for ΔR608 and a different mutation, however, tended to have either moderate or severe disease, suggesting that these other missense mutations, namely H567L, P475L, R496L, R441X, R600H, W391G, and H425K, are more deleterious.

CONCLUSIONS

Serial evaluations of 29 patients with NPD-B provided information on the natural history of the disease. Leukopenia and thrombocytopenia tended to worsen over time, and the atherogenic lipid profile tended to remain markedly abnormal despite some normalization of the triglyceride level. In addition, pulmonary function gradually worsened, and serum transaminases remained elevated. Unfortunately, many features of this progressive disease are not amenable to any available therapies. It is therefore hoped that future efforts directed at correcting the underlying metabolic abnormality, such as enzyme replacement or gene therapy, may prove effective at treating the hematologic, lipid, pulmonary, and hepatic abnormalities in this disorder.

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