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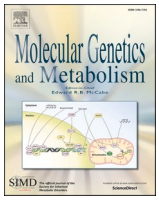
Molecular Genetics and Metabolism 139 (2023) 107631

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Glycoprotein non-metastatic protein B (GPNMB) plasma values in patients with chronic visceral acid sphingomyelinase deficiency

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ARTICLE INFO

Keywords:
Acid sphingomyelinase deficiency (ASMD)
Niemann-Pick disease type B
Glycoprotein non-metastatic protein B (GPNMB)
Biomarkers

ABSTRACT

Acid sphingomyelinase deficiency (ASMD) is a rare LSD characterized by lysosomal accumulation of sphingomyelin, primarily in macrophages. With the recent availability of enzyme replacement therapy, the need for biomarkers to assess severity of disease has increased. Glycoprotein non-metastatic protein B (GPNMB) plasma levels were demonstrated to be elevated in Gaucher disease. Given the similarities between Gaucher disease and ASMD, the hypothesis was that GPNMB might be a potential biochemical marker for ASMD as well.

Plasma samples of ASMD patients were analyzed and GPNMB plasma levels were compared to those of healthy volunteers. Visceral disease severity was classified as *severe* when splenic, hepatic and pulmonary manifestations were all present and as *mild to moderate* if this was not the case.

Median GPNMB levels in 67 samples of 19 ASMD patients were 185 ng/ml (range 70–811 ng/ml) and were increased compared to 10 healthy controls (median 36 ng/ml, range 9–175 ng/ml, $p < 0.001$). Median plasma GPNMB levels of ASMD patients with mild to moderate visceral disease compared to patients with severe visceral disease differed significantly and did not overlap (respectively 109 ng/ml, range 70–304 ng/ml and 325 ng/ml, range 165–811 ng/ml, $p < 0.001$). Correlations with other biochemical markers of ASMD (i.e. chitotriosidase activity, CCL18 and lysosphingomyelin, respectively $R = 0.28$, $p = 0.270$; $R = 0.34$, $p = 0.180$; $R = 0.39$, $p = 0.100$) and clinical parameters (i.e. spleen volume, liver volume, diffusion capacity and forced vital capacity, respectively $R = 0.59$, $p = 0.061$, $R = 0.5$, $p = 0.100$, $R = 0.065$, $p = 0.810$, $R = -0.38$, $p = 0.160$) could not be established within this study.

The results of this study suggest that GPNMB might be suitable as a biomarker of visceral disease severity in ASMD. Correlations between GPNMB and biochemical or clinical markers of ASMD and response to therapy have to be studied in a larger cohort.

1. Introduction

Acid sphingomyelinase deficiency (ASMD, OMIM 607616), also known as Niemann-Pick disease types A and B, is a lysosomal storage disorder (LSD) caused by mutations in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene. The encoded protein, acid sphingomyelinase (ASM, EC 3.1.4.12), is a lysosomal enzyme required for the breakdown of sphingomyelin into phosphocholine and ceramide. Impaired catalytic capacity of ASM results in accumulation of sphingomyelin, which is most prominently observed in the lysosomes of macrophages. ASMD is clinically heterogeneous with manifestations ranging from a severe infantile form with neurological symptoms leading to death often before

Abbreviations: ADAM10, A Disintegrin And Metalloproteinase 10; ASM, acid sphingomyelinase; ASMD, Acid sphingomyelinase deficiency; CCL18, chemokine C—C motif ligand 18; DLCO, diffusion capacity of the lung for carbon monoxide; ELISA, enzyme-linked immunosorbent assay; ERT, enzyme replacement therapy; FVC, forced vital capacity; GPNMB, Glycoprotein non-metastatic protein B; HRCT, high-resolution computed tomography; LSD, lysosomal storage disorder; lysoSM, lysosphingomyelin.

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https://doi.org/10.1016/j.ymgme.2023.107631
Received 27 March 2023; Received in revised form 23 June 2023; Accepted 23 June 2023
Available online 9 July 2023

the age of three years, to an intermediate phenotype with both visceral and neurological involvement and survival into childhood or adolescence, to a late-onset form with solely visceral pathology (1,2). The main visceral manifestations of ASMD are hepatosplenomegaly, frequently accompanied by thrombocytopenia and interstitial lung disease, which leads to decreased diffusion capacity in severe cases (3,4). Moreover, dyslipidemia, anemia, leukopenia, decreased bone mineral content and decreased bone mineral density have been described in ASMD patients (4,5).

Enzyme replacement therapy (ERT) for ASMD (olipudase alfa™, Sanofi Genzyme) has recently been authorized in the EU and the USA as therapy for the visceral manifestations of ASMD (6,7). Since the disease can be stable and very mild over decades in some adult patients, it has been proposed that treatment should be reserved for individuals with significant signs of disease as is done in other LSDs for which therapy has been available for a longer period of time (8,9). For those who might benefit from ERT, accurate timing of initiation of therapy is currently unknown. Thus, assessment of disease burden and prediction of future complications are of importance. For this purpose, biomarkers may be helpful (10,11). Biomarkers are disease parameters that serve as indicators of biological processes associated with clinical manifestations, outcome or treatment responsiveness (12).

In the search for biomarkers, the pathophysiological resemblance of ASMD to Gaucher disease (OMIM 230800), a well characterized LSD, is helpful. Similar to ASMD, visceral Gaucher disease is characterized by the presence of lipid laden macrophages in spleen and liver, so called Gaucher cells. Biomarkers have been studied extensively in Gaucher disease. The Gaucher cells massively produce and secrete chitotriosidase, a chitinase elevated in patient plasma that is applied as a biomarker. An alternative Gaucher plasma biomarker is the chemokine C—C motif ligand 18 (CCL18) being likewise secreted by storage cells. Plasma chitotriosidase and CCL18 were found to be indicative for disease burden and can aid in the decision on timing and dosing regimen of treatment (13,14).

The membrane protein glycoprotein non-metastatic protein B (GPNMB, alternatively called osteoactivin) was also found to be abundant in Gaucher cells (15–17). GPNMB is highly expressed in macrophages and has been studied in the context of diseases including melanoma, other types of cancer, neurodegenerative diseases and obesity (17,18). GPNMB is secreted by M2 macrophages and plays a role in several anti-inflammatory processes, such as wound repair (19,20). Its luminal domain may be cleaved by A Disintegrin And Metalloproteinase 10 (ADAM10) causing release into the circulation (21). GPNMB is thought to be upregulated due to lysosomal stress and to play a protective role in maintaining lysosomal integrity (22). Elevation of plasma GPNMB levels and upregulation of GPNMB were demonstrated in diseases associated with lysosomal dysfunction in macrophages, specifically Gaucher disease and Niemann-Pick type C disease (16,23–25). Furthermore, it was suggested that plasma GPNMB levels may serve as marker for disease severity in Gaucher disease (16,23). Of note, GPNMB is known to be highly expressed in M2-polarized macrophages rather than M1 macrophage, and GPNMB promotes anti-inflammatory M2 polarization on macrophages (18,26). In addition, evidence has recently been presented that plasma GPNMB may act as a potent inducer of immunosuppression in cancer by dampening T-cell responses; for a recent review see reference 16 (16).

GPNMB has not yet been studied in the context of ASMD. Therefore, this study aims to assess GPNMB plasma levels in patients with chronic visceral ASMD, to compare them to GPNMB plasma levels of healthy controls and Gaucher patients and to discuss the utility of GPNMB as a biomarker for ASMD.

2. Materials and methods

2.1. Participants

All patients with a biochemically and genetically proven diagnosis of ASMD were included. Plasma samples were taken at the yearly outpatient visits and stored in a biobank. Patients (or parents in case of children) gave written informed consent for the use of plasma samples to answer future research questions. Beside patient samples, rest material of healthy controls collected within other studies was stored in the biobank as well. Healthy controls included in this study were defined as healthy based on their medical history and medication use. The biobank was approved by the Biobank Review Committee of the Amsterdam UMC, location AMC (2014_192).

2.2. Biochemical analyses

Plasma samples were stored at −80 °C. Storage period varied but was at least six months. A commercial kit (R&D, DY2550) was used for sandwich enzyme-linked immunosorbent assay (ELISA) measurements according to manufacturer's instructions. Shortly, plasma was centrifuged for 10 min at 11.000 rcf at 4 °C and clear layer was diluted a hundred times in BSA containing reagent diluent. A capture antibody was used to immobilize GPNMB from 100× diluted plasma from ASMD patients and healthy controls, and 400× diluted plasma from Gaucher patients on a pre-blocked plate. Subsequently a biotin-conjugated antibody was used to bind captured GPNMB and a streptavidin-horseradish peroxidase (HRP) was employed for enzymatic detection. Recombinant GPNMB in known concentration provided by the kit was used as standard to quantify plasma GPNMB levels. Measurements were performed in technical *duplo* and the ELISA measurements were repeated three times.

Chitotriosidase activity levels were measured in plasma with 4-methylumbelliferyl-deoxychitobiose substrate as previously described (27). In case of heterozygosity for the common 24-base-pair duplication in the *CHIT1* gene, chitotriosidase activity was doubled (27). Plasma CCL18 levels were measured by ELISA using a commercially available CytoSet (Biosource International, Camarillo, CA), as described previously (28). Lysosphingomyelin (lysoSM) plasma levels were measured by extracting sphingolipids from plasma and analysis with LC-MS/MS as described previously (29).

2.3. Definitions and statistical analysis

Median plasma GPNMB levels were calculated when more than one plasma sample was available for an individual ASMD patient. Severity of visceral manifestations of ASMD was categorized as *severe* or *mild to moderate*, neurological manifestations were not taken into account for this classification. Severe visceral disease was defined as presence of splenic, hepatic and pulmonary manifestations, respectively defined as: extensive splenomegaly (spleen volume $>$ 1000 ml) or thrombocytopenia ($<$ 150 10^9/l)), hepatomegaly (liver volume $>$ 2500 ml) or increased AST- or ALT levels (according to local reference values) and decreased diffusion capacity of the lung for carbon monoxide (DLCO, $<$ 80% of predicted), decreased forced vital capacity (FVC, $<$ 80% of predicted) or signs of interstitial lung disease on high-resolution computed tomography (HRCT) or X-ray. Mild to moderate visceral disease was defined as the absence of disease manifestations in one or more of the organ systems as defined above. Groups were compared using the Wilcoxon signed rank test. Correlation analyses were performed using Spearman's rank correlation. Data were analyzed with RStudio (version 4.0.3).

3. Results

In total 67 plasma samples of 19 ASMD patients and ten plasma

Table 1
Amount of GPNMB samples and clinical characteristics of ASMD patients. [1]Splenomegaly > 1000 ml or thrombocytes <150 10^9/l, [2]Hepatomegaly > 2500 ml or increased ALT- or AST levels, [3]DLCO < 80%, FVC < 80% or signs of ILD on HRCT or X-ray, *organomegaly established on sonography. GPNMB: Glycoprotein non-metastatic protein B, DLCO: diffusion capacity of the lung for carbon monoxide, FVC: forced vital capacity, ILD: interstitial lung disease, HRCT: high-resolution computed tomography, ASMD: acid sphingomyelinase deficiency, M: male, F: female.

ID	Age at first GPNMB measu-rement	Age at last GPNMB measu-rement	GPNMB samples (n)	(median) GPNMB plasma level	sex				severity of visceral manifesta-tions of ASMD
						splenic manifestations[2]	hepatic manifestations[1]	pulmonary manifestations[3]	
1	9	13,3	6	407	M	yes*	yes*	yes	severe
2	12	15,1	4	336	F	yes*	yes*	yes	severe
3	17,6	18,7	2	811	F	yes	yes	yes	severe
4	17,6	23,5	6	325	M	splenectomy at age 21	yes	yes	severe
5	19		1	110	F	yes*	no*	yes	mild-moderate
6	20,1	21,4	2	304	M	yes	no	yes	mild-moderate
7	22,8	–	1	108	F	no	no	yes	mild-moderate
8	25,6	25,9	2	165	M	yes	yes	yes	severe
9	37	40,3	4	273	M	yes	yes	yes	severe
10	38,6	42,5	3	145	F	no	no	yes	mild-moderate
11	40,2	–	1	359	M	yes	yes	yes	severe
12	40,4	47	6	249	M	yes	yes	yes	severe
13	40,8	–	1	89	M	no	yes	no	mild-moderate
14	43,6	50,4	3	273	M	yes	yes	yes	severe
15	43,7	46	3	105	F	no	no	yes	mild-moderate
16	49,1	55,8	6	77	M	yes	no	no	mild-moderate
17	49,3	55	4	185	M	yes	yes	no	mild-moderate
18	59,6	–	1	70	F	yes	no	yes	mild-moderate
19	64,2	–	1	142	F	yes	no	yes	mild-moderate

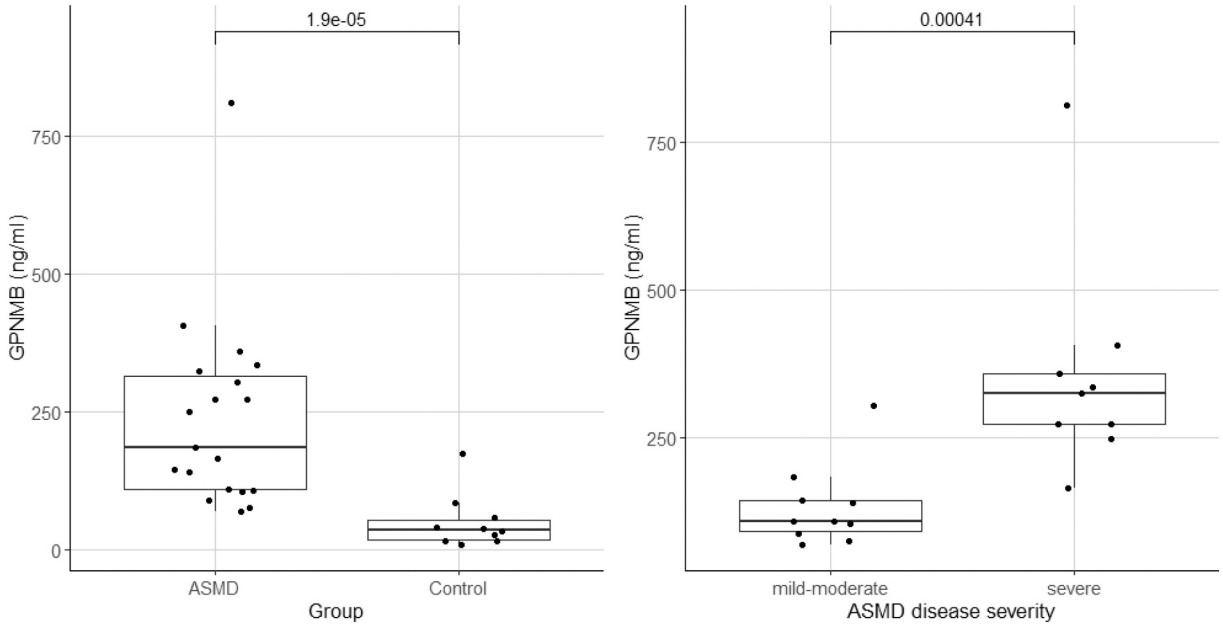

Fig. 1. Comparison of GPNMB plasma values between ASMD and controls and between mild to moderate and severe visceral ASMD. For ASMD patients the median GPNMB value is plotted if multiple samples were available. The Wilcoxon signed rank test was used to compare groups. GPNMB: Glycoprotein non-metastatic protein B, ASMD: acid sphingomyelinase deficiency.

samples of ten healthy controls were available. All 19 ASMD patients had the chronic visceral subtype, which means none of the patients had neurological manifestations. All patients were from different families, consanguinity was present in five families. Patients' age at the time of sample collection ranged from 9 to 64 years old, healthy controls were between 20 and 24 years old. Per patient between one and six plasma samples were available for analysis. Clinical characteristics of the ASMD patients are depicted in Table 1,

Median GPNMB plasma levels in ASMD patients were 185 ng/ml (range 70–811 ng/ml), healthy controls had a median GPNMB level of 36 ng/ml (range 9–175 ng/ml, $p < 0.001$) (Fig. 1). ASMD patients with severe visceral disease ($n = 9$) had a median GPNMB plasma level of 325 ng/ml (165–811 ng/ml), while patients with mild to moderate visceral disease ($n = 10$) had a median GPNMB plasma level of 109 ng/ml (70–304 ng/ml, $p < 0.001$) (Fig. 1).

GPNMB plasma levels of ASMD patients were also compared with GPNMB plasma levels of Gaucher patients ($n = 8$, 8 samples) to serve as a positive control. GPNMB levels in Gaucher were on average over 5-fold higher than in ASMD (median 1121 ng/ml, range 408–2050, $p < 0.001$, see supplemental figure).

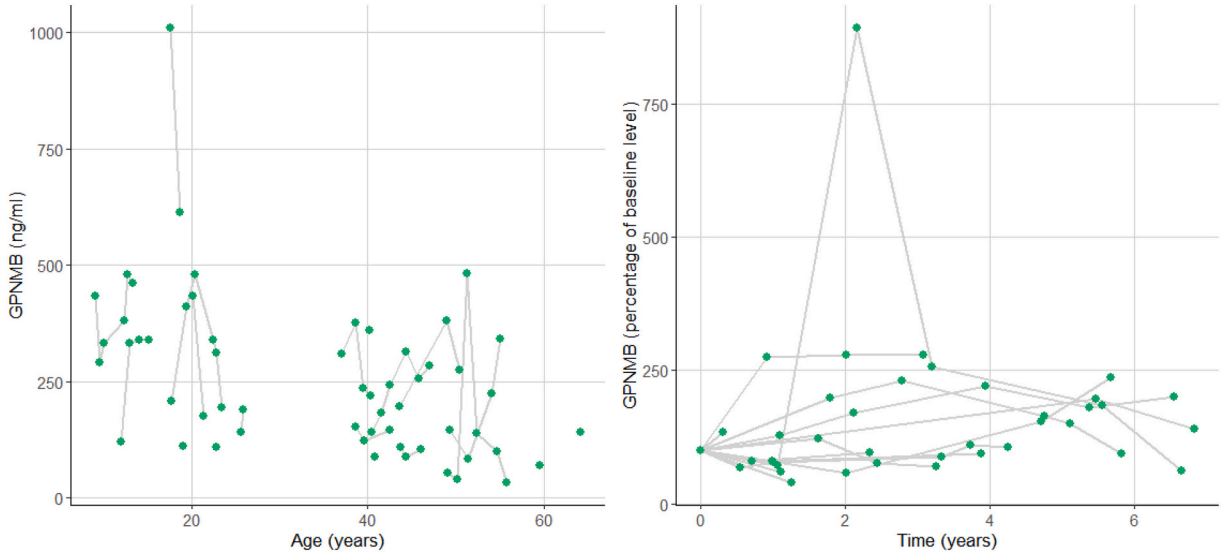

Fig. 2. GPNMB plasma values of ASMD patients. Left: GPNMB levels plotted against age per individual patient. Right: for patients with more than one sample the variation of GPNMB is plotted against time with baseline value at 100%. GPNMB: Glycoprotein non-metastatic protein B, ASMD: acid sphingomyelinase deficiency.

GPNMB plasma levels measured within this study were stable over time (Fig. 2). Variation of GPNMB levels as compared to baseline level was between 50% and 250% for 84% of the measurements of patients with follow-up samples ($n = 13$, Fig. 2).

Relations between GPNMB plasma levels and clinical and biochemical markers of ASMD were studied. One GPNMB measurement of one ASMD patient (ID 3) was excluded from these analyses because it was considered an outlier. No correlations between GPNMB and spleen volume ($R = 0.59$, $p = 0.061$), liver volume (R = 0.5, $p = 0.100$), DLCO ($R = 0.065$, $p = 0.810$) or FVC ($R = -0.38$, $p = 0.160$) were present (Fig. 3). No significant correlation was present between GPNMB and plasma chitotriosidase activity ($R = 0.28$, $p = 0.270$), CCL18 plasma levels ($R = 0.34$, $p = 0.180$) or lysoSM plasma levels ($R = 0.39$, p = 0.100) either (Fig. 3).

4. Discussion

To the best of our knowledge, this is the first study showing that GPNMB levels are significantly higher in ASMD patients compared to healthy controls. Moreover, GPNMB levels in ASMD patients with severe visceral manifestations were higher compared to GPNMB levels of patients with mild to moderate visceral symptoms. Plasma GPNMB levels seem to be stable over time. Lastly, GPNMB levels were significantly lower in ASMD patients compared to Gaucher patients.

GPNMB has been studied in the context of other LSDs. In a mouse model for Niemann-Pick type C, an LSD with highly similar pathology, GPNMB plasma levels are increased and respond to experimental therapy (24,30). As mentioned in the introduction and demonstrated in this study, plasma GPNMB levels are elevated in Gaucher disease as well (15–17). Moreover, treatment of Gaucher patients with ERT and SRT resulted in reduction of plasma GPNMB levels (23,31) and plasma GPNMB levels of Gaucher patients were demonstrated to correlate with chitotriosidase activity, CCL18 and glucosylceramide levels (16).

Our study rendered several findings supporting the use of plasma GPNMB to monitor ASMD. Firstly, plasma GPNMB levels correlated with the severity of visceral disease manifestations: patients with disease manifestations in spleen, liver and lungs had higher GPNMB levels than patients with manifestations in one or two organ systems. Significant correlations with biochemical markers or markers of specific organ systems were not noted. Future investigation of a larger cohort of patients might reveal some specific correlations, especially for spleen volume. Secondly, healthy controls and ASMD patients could be distinguished based on plasma GPNMB levels, although an outlier within the controls was identified. It should be stressed that excessive GPNMB in ASMD patients likely derives from lipid-laden macrophages and consequently does not reflect one specific symptom but rather total visceral disease burden. In other words, plasma GPNMB, like plasma chitotriosidase, is a biomarker of the lipid laden macrophages in ASMD patients. This also holds for Gaucher disease and its storage macrophage derived biomarkers. Strictly speaking, plasma GPNMB acts as biomarker of pathological storage cells rather than specific ASMD symptoms.

Advantages of GPNMB compared to currently used biochemical markers are that measurements of GPNMB by ELISA are easy to perform, which might make GPNMB measurement more widely applicable than for instance enzyme activity assays as necessary for chitotriosidase activity measurement. Moreover, GPNMB could be of added value in preclinical studies since both chitotriosidase activity and CCL18 cannot be used as biomarkers in mouse models (16).

GPNMB plasma levels were 5-fold higher in Gaucher patients than in ASMD patients. This is in line with the higher plasma levels of chitotriosidase activity that are found in Gaucher patients compared to ASMD patients (10). An explanation could be the origin of plasma GPNMB and chitotriosidase, which is excretion by storage macrophages. Macrophages are the main storage cell in both diseases, storage macrophages seem to be more abundant in Gaucher disease which is illustrated by the similar but more pronounced clinical and biochemical abnormalities in Gaucher disease as compared to ASMD.

A limitation of this study is the small sample size. All patients have chronic visceral disease, but still show different clinical manifestations ranging from mild to severe. This makes the population both small and heterogeneous. However, since all adult ASMD patients in the Netherlands were included, this is a reflection of the real world population.

In conclusion, future use of GPNMB as a biomarker of ASMD is promising, but should be studied more in-depth. As suggested previously, a panel of biomarkers should be used to assess disease severity and try to predict course of disease in ASMD patients (10). GPNMB could be of additional value within such a panel. An interesting and important addition would be to study the patients' response to therapy with respect to plasma GPNMB.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2023.107631.

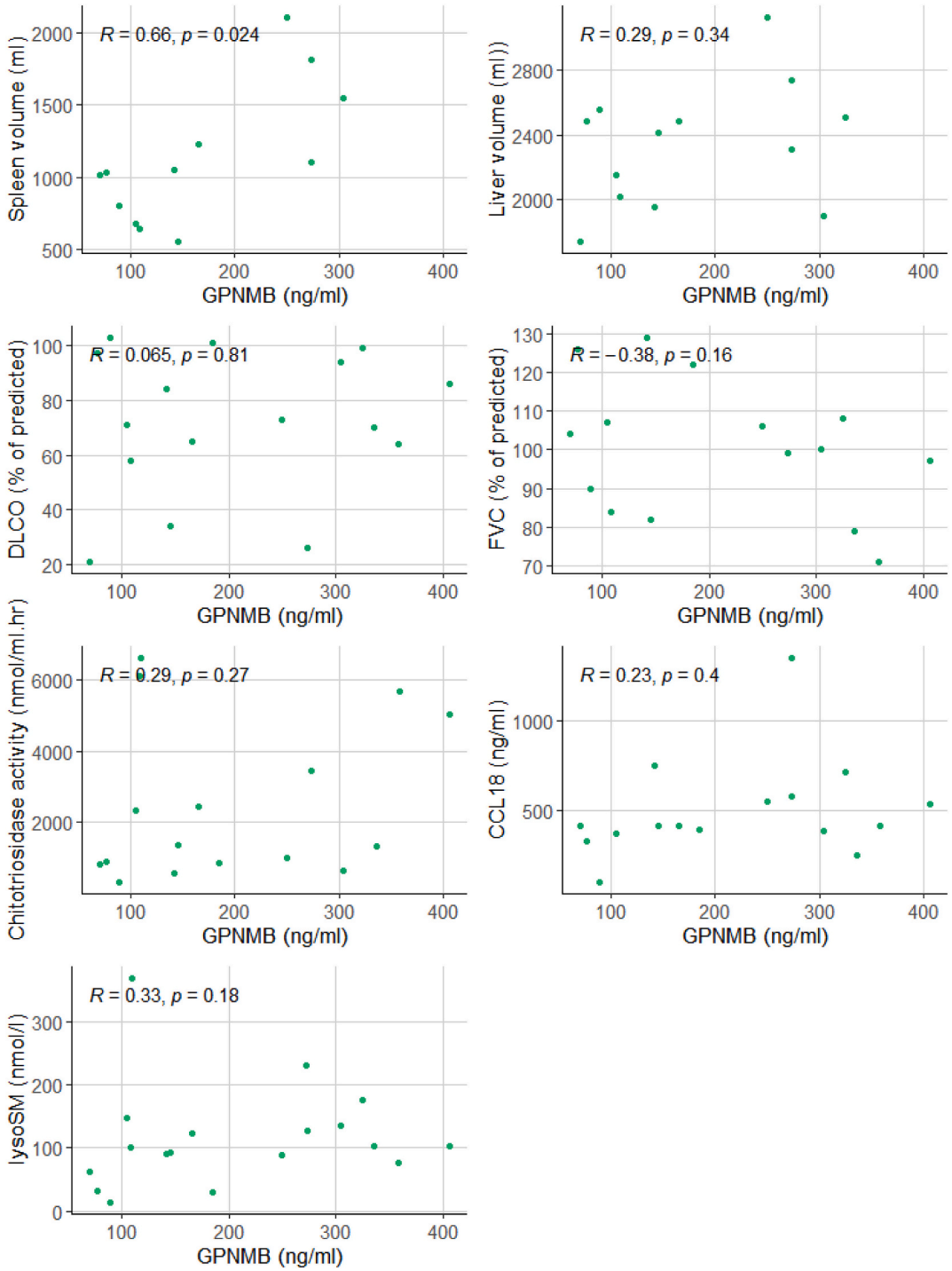

Fig. 3. Correlation plots of GPNMB with biochemical and clinical markers of ASMD. GPNMB: Glycoprotein non-metastatic protein B, ASMD: acid sphingomyelinase deficiency, CCL18: chemokine ligand 18, lysoSM: lysosphingomyelin, DLCO: diffusion capacity of the lung for carbon monoxide, FVC: forced vital capacity.

Declaration of Competing Interest

ML, LV, MB and JA have no competing interests to declare. EE is involved in a pre-marketing study with Sanofi Genzyme. CH is involved in premarketing studies with Sanofi Genzyme, Protalix, Cheisi and Idorsia. BS was involved in pre-marketing studies with Protalix, Cheisi and Sanofi Genzyme. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

Data will be made available on request.

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