

Chronic acid sphingomyelinase deficiency diagnosed in infancy/childhood in Polish patients: 2024 update

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Abstract

Background. Acid sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal storage disease (LSD) associated with biallelic pathogenic variants in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene.

Objectives. The aim of this study was to provide the 2024 update on chronic visceral and neurovisceral ASMD diagnosed in the infancy/childhood in Polish patients.

Materials and methods. All the patients diagnosed in the pediatric age (0–18 years) with ASMD, both chronic neurovisceral and visceral type, and then systematically followed up, were enrolled into the study.

Results. A total number of 7 patients were enrolled into the study. Four patients were previously reported. Two patients were newly recognized with ASMD – 1 with chronic visceral and 1 with chronic neurovisceral ASMD. Splenomegaly was noted in all the patients while a mild liver enlargement was observed in 4 of 7 patients. All patients presented with decreased high-density lipoprotein cholesterol (HDL-C) and decreased serum 25-hydroxy-vitamin D concentration while almost all (6 of 7) with hypercholesterolemia. Cherry-red spot was observed in 5 of 7 patients, including 1 patient with neurovisceral type. Seven various *SMPD1* gene variants were identified and missense variants were the most common types of genetic lesions, comprising 71% of all alleles. In all the screened patients, lyso-sphingomyelin (lyso-SM) in dried blood spot (DBS) was found elevated; however, the greater values were observed for patients with chronic neurovisceral type.

Conclusions. Chronic acid sphingomyelinase deficiency (ASMD) is a slowly progressive disease. Pediatric ASMD is characterized by spleno-hepatomegaly, dyslipidemia (with decreased HDL-C as the most characteristic) and infiltrative (interstitial) lung disease. Both visceral and neurovisceral chronic ASMD patients could present with cherry-red spot. Both acid sphingomyelinase activity and lyso-sphingomyelin concentration in DBS should be regarded as a first-tier screening method into ASMD.

Key words: children, lysosomal storage disease, acid sphingomyelinase deficiency, lyso-sphingomyelin, dried blood spot

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Background

Acid sphingomyelinase deficiency (ASMD), due to biallelic pathogenic variants in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene (MIM #607608), is an autosomal recessive lysosomal storage disease (LSD) associated with accumulation of lysosomal sphingomyelin.¹

The original Niemann–Pick type A (MIM # 257200) disease is currently classified as the infantile neurovisceral ASMD, while Niemann–Pick type B (# 607616) disease is referred to as the chronic visceral type, and Niemann–Pick type A/B as the chronic neurovisceral type.^{2,3} Infantile neurovisceral ASMD constitutes a neuronopathic (neurodegenerative), rapidly progressing, and fatal disorder while chronic visceral ASMD is a non-neuronopathic, slowly progressive and visceral disorder.^{2,3} Infants with neurovisceral ASMD typically present with delayed psychomotor development followed by its regression (clinically noted in the 2nd 6 months of life). Neurological features are accompanied by massive hepatosplenomegaly, failure to thrive, and recurrent respiratory tract infections. Patients with visceral ASMD do not present neurological features, but the somatic phenotype is very heterogeneous. The most common signs and symptoms include hepatosplenomegaly (sometimes associated with thrombocytopenia), elevated serum transaminases (mildly-to-moderately), dyslipidemia, and interstitial lung disease (based on radiological features). An intermediate neurological phenotype (slowly progressive neurological disease) with somatic (visceral) manifestations similar to type B, underlines the chronic neurovisceral ASMD.^{2–4} In this group of ASMD patients, the onset of neurological symptoms occurs later in life than in patients with infantile neurovisceral form, but is usually noted in childhood. The most commonly reported symptoms include a mild hypotonia and/or hyporeflexia.

In December 2020, enzyme replacement therapy (ERT) with recombinant human ASM (olipudase alfa) was approved by the European Medicines Agency (EMA) for the treatment of the non-neurological manifestations of ASMD.⁵ Enzyme replacement therapy has become available in Poland since April 2024 (as part of a drug program financed by the National Health Fund). The eligibility criteria for children with ASMD in the drug program, in addition to those included in the EMA registration, include the need for a spleen volume that is at least 5 times the normal volume as measured by a magnetic resonance imaging (MRI) scan.

Objectives

In 2018, we published a single-center study comprising 16 patients (both children and adults) with chronic visceral ASMD (formerly known as Niemann–Pick type B) who were diagnosed and followed up at the Children's

Memorial Health Institute (Warsaw, Poland).⁶ Since then, several novel patients, including 2 children, have been diagnosed. In April 2024, an enzyme replacement therapy with olipudase alfa became available for patients with ASMD in Poland.

The aim of this study was to provide the 2024 update on chronic visceral and neurovisceral ASMD diagnosed in the infancy/childhood in Polish patients.

Patients and methods

Study design, setting and participants

All the patients diagnosed in the pediatric age (0–18 years) with ASMD, both chronic neurovisceral and visceral type, and then systematically followed up, were enrolled into the study. A retrospective chart review of the patients' medical records was performed.

Variables: ASM activity, *SMPD1* gene sequencing and biomarkers

Acid sphingomyelinase deficiency was diagnosed through the demonstration of reduced ASM activity in peripheral blood leukocytes or dried blood spot (DBS) and confirmed by identification of *SMPD1* pathogenic variants. Acid sphingomyelinase activity in leukocytes was measured with the 2-N-hexadecanoylamino-4-nitrophenylphosphorylcholine as a substrate.⁷ Chitotriosidase (ChT) activity was measured in plasma samples using a spectrofluorometric method as presented by Holak et al.⁸ Dried blood spot tests were performed as suggested by the producer (ARCHIMED Life Science GmbH, Vienna, Austria). ARCHIMEDlife laboratory has been certified with ISO 15189 (Medical Laboratory* – Clinical Chemistry to Genetics), ISO 9000 (Quality Management System), ISO 13485 (Medical Devices – IVD Development and Production) and GLP-lab certificate fully integrated for clinical studies. According to the laboratory information, the sample was analyzed as previously described.⁹

Results

A total number of 7 patients (3 men and 4 women) were enrolled into the study. The characteristics of individual patients are presented in Table 1. Four patients were previously reported.⁶ Two patients were newly recognized with ASMD – 1 with chronic visceral type (Patient (Pt) 3) and 1 with chronic neurovisceral type (Pt 2). The last patient (Pt 6) was not previously (2018 year) reported due to a diagnosis of chronic neurovisceral type of ASMD.

Three patients from 1 family were of Romani descent (currently living in foster care) and were diagnosed through family screening (at 12 months, 1.5 years and 5 years of age,

Table 1. Clinical, biochemical and molecular characteristics of the study patients

Patient No.	Genotype	Age [years]	Lyso-SPM [ng/mL] <70	ChT [nmol/mL/h] <150	Liver length in midclavicular line [mm]	Spleen longitudinal length [mm]	Platelets [1000/ μ L] <150	AST [IU/L] <45	ALT [IU/L] <40	TC [mg/dL] <200	LDL-C [mg/dL] <115	HDL-C [mg/dL] 32–63	TG [mg/dL] 44–197	25-OH-D [ng/mL] >30
1	Hmz; c.880C>A, p.Gln294Lys	5	490.8	620	100	110	161	48	18	175	123	27	125	24
2	c.748A>C, p.Ser250Arg/ c.1092-1G>C, p.?	1	294.9	960	80	110	121	212	160	235	149	19	331	24
		2	813.5	1080	125	165	118	130	150	210	125	17	288	15
3	Hmz; c.1177T>G, p.Trp393Gly	1	n.a.	36	50	85	255	160	138	220	130	20	350	n.a.
		3	n.a.	2048	110	130	300	49	46	208	140	21	230	17
		5	279	1540	130	180	236	44	32	213	156	20	182	22
4	Hmz; c.1177T>G, p.Trp393Gly	1.5	n.a.	n.a.	110	90	330	1,200	580	186	120	9	300	36
		3	n.a.	488	120	115	230	470	370	206	138	18	250	24
		8	367	360	150	210	153	46	30	219	158	17	220	9
5	Hmz; c.1177T>G, p.Trp393Gly	5	n.a.	296	100	120	256	77	65	243	145	45	270	12
		13	303	n.a.	160	150	259	95	25	220	160	39	106	18
		15	378	n.a.	190	180	238	37	23	192	120	34	191	10
6	c.880C>A, p.Gln294Lys/ c.1758_1786del, p.Ala597Profs*7	2.5	n.a.	2000	135	165	191	57	17	121	93	13	75	21
		6	n.a.	3500	150	190	162	64	35	128	87	18	113	21
		10	756	n.a.	160	200	97	42	39	150	90	17	124	17
7	c.581dup, p.Ala195Serfs*14/ c.1829_1831del, p.Arg610del	3	n.a.	n.a.	10 cm below costal margin	5 cm below costal margin	222	38	20	253	n.a.	n.a.	242	n.a.
		13	n.a.	n.a.	8 cm below costal margin	10 cm below costal margin	240	35	30	270	n.a.	n.a.	220	n.a.
		20	n.a.	908	145	165	180	20	22	n.a.	186	n.a.	162	n.a.
		35	n.a.	n.a.	150	180	138	25	30	235	205	20	195	n.a.
		45	309	n.a.	180	180	127	35	30	278	194	25	298	13.4

n.a. – not analyzed; hmz – homozygote; ChT – chitotriosidase; AST – aspartate aminotransferase; ALT – alanine aminotransferase; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TC – total cholesterol; TG – triglycerides.

respectively) – 2 older brothers had died (the primary cause of death was not related to ASDM).⁶ Four other patients were of Polish origin and were diagnosed at 12 months, 2.5 years, 5 years, and 3 years of age, respectively. Six of the 7 patients underwent routine clinical evaluation. Follow-up of the study patients ranged from 1 to 42 years.

On the basis on clinical and molecular characteristics, the chronic visceral type of ASDM was diagnosed in 5 patients, while 2 others (Pt 2 and Pt 6) were diagnosed with chronic neurovisceral ASDM. Patient 2 presented with a slightly delayed psychomotor development and based on genetic results – 2 *SMPD1* variants (in-trans): c.748A>C (p.Ser250Arg) and c. c.1092-1G>C associated with Niemann–Pick type A disease (Table 2). Patient 6 presented with psychomotor regression since the age of 3 years and developed epilepsy at the age of 6–7 years. He was found to be a homozygote for c.880C>A (p.Gln294Lys) variant associated with the intermediate type.

Splenomegaly was noted in all the patients, while a mild liver enlargement was observed in 4 of 7 patients at the time of ASDM diagnosis. A gradual enlargement of both organs, spleen and liver, was observed during clinical monitoring (Table 1). Elevated serum aspartate aminotransferase (AST) was observed in 6 of 7 patients while elevated serum alanine aminotransferase (ALT) was observed in 3 of 7 patients at the time of diagnosis. The value of serum transaminases was found to be several-fold above the upper limit of normal values (Table 1). A decrease (to normalization) of serum transaminases was observed during follow-up.

Only 1 patient (Pt 2 with chronic neurovisceral type) presented with thrombocytopenia (defined as platelets below 150,000/ μ L) at the time of diagnosis. Two other patients (Pt 6 with chronic neurovisceral type and Pt 7 with chronic visceral type) developed thrombocytopenia at the age of 10 years and 35 years, respectively.

Table 2. *SMPD1* variants in the study group according to ClinVar

<i>SMPD1</i> variant	Molecular consequence	Protein change	Condition
c.1177T>G	missense variant	p.Trp393Gly	Niemann–Pick disease, type B
c.880C>A	missense variant	p.Gln294Lys	Niemann–Pick disease, intermediate, protracted neurovisceral
c.1092-1G>C	splice acceptor	Non applicable	Niemann–Pick disease, type A
c.1785_1786del	frameshift variant	p.Ala597fs	Niemann–Pick disease, type A
c.748A>C	missense variant	p.Ser250Arg	Niemann–Pick disease, type A
c.581dup	frameshift variant	p.Ala195Serfs*14	Niemann–Pick disease, type A; Niemann–Pick disease, type B
c.1829_1831del	inframe deletion	p.Arg610del	Niemann–Pick disease, type B

Elevated total serum cholesterol and LDL cholesterol as well as triglycerides were noted in 6 of 7 patients, while decreased HDL cholesterol was observed in all patients. Decreased serum 25-hydroxyvitamin D concentrations were also observed in all patients (Table 1). Cherry-red spot was described in 5 of 7 patients at the time of ASMD diagnosis, including 1 patient with neurovisceral type.

All patients were diagnosed with interstitial lung disease by chest X-ray or computed tomography (CT). Except for frequent respiratory tract infections in infancy/early childhood reported in all patients, no clinical consequences (normal spirometry in all 3 diagnosed patients) of pulmonary macrophage involvement in childhood/adolescence were observed. The last patient (Pt 7), who was followed for almost 42 years, was diagnosed with restrictive lung disease at 20 years of age.

Data on ASM activity were available for all (7) patients (5 in peripheral blood leukocytes and 2 in DBS). In case of 1 patient (Pt 6), ASM activity in leukocytes was found normal; however, due to strong clinical suspicion (and excluding Gaucher disease; GD), the final diagnosis of ASMD was established by molecular analysis of the *SMPD1* gene. This patient was found to be heterozygous for Q292K *SMPD1* variant (and deletion on the 2nd allele). Seven various *SMPD1* gene variants (Table 2) were identified in the study group, and missense variants were the most common types of genetic lesions, comprising 71% of all alleles.

At the time of diagnosis, the lyso-sphingomyelin (lyso-SM) value in DBS was available only for 2 patients, while 6 patients underwent follow-up assessment (Table 1). In all patients with ASMD, lyso-SM was found elevated, however, the greater values were observed in patients with chronic neurovisceral type.

Chitotriosidase activity in serum was available for all 6 patients, however, in 4 of them subsequent analyses were performed. It decreased in 2 of them and increased in 2 others (neurovisceral type).

Discussion

The paper described the 2024 update on ASMD in Poland from pediatric perspective. It provides a clinical, biochemical and molecular characteristics of 7 Polish patients with chronic visceral and neurovisceral ASMD who were diagnosed in the infancy/childhood and systematically followed up.

With the growing awareness of rare diseases, including inherited metabolic diseases (IMD), and the greater availability of diagnostic methods, including routine assessment of lyso-sphingolipids as biomarkers in LSD, but most importantly next-generation sequencing (NGS) technology, new patients with known diseases and novel diseases are being discovered.¹⁰ Only last year (2023), 2 pediatric patients with chronic ASMD were diagnosed in Poland. This is of great importance in the context of enzyme replacement therapy that has only recently become available in Poland.

The clinical and biochemical features of the presented cohort of pediatric patients with ASMD are consistent with those reported in the literature. Children with ASMD typically present with hepatosplenomegaly accompanied by elevated serum transaminases, dyslipidemia and radiological features of interstitial lung disease.

Based on the data presented and those from the literature, we recommend that all children with splenomegaly (with or without hepatomegaly) of unknown cause should undergo ASM analysis. Thrombocytopenia was not a frequent abnormality in chronic ASMD as opposed to GD, in which it is usually found in almost all patients.¹¹ The characteristic feature of pediatric patients with ASMD, especially in infancy and early childhood, is elevated serum transaminases activity, with a tendency to normalize in older children. The exact cause of normalization of serum transaminases is not known; however, progression to hepatic fibrosis is observed in the natural history of liver disease in ASMD.¹² Dyslipidemia was also found to be a unique biochemical feature of chronic ASMD; however, the similar pattern is observed in lysosomal acid lipase

deficiency.^{11,13} A quite interesting abnormality was a decreased 25-hydroxy-vitamin D level found in all patients with ASMD. It is a well-known phenomenon observed in GD patients (and other LSD), with no exact explanation.¹⁴ Radiographic evidence of infiltrative (interstitial) lung disease was noted in all children with chronic ASMD. Besides frequent respiratory tract infections in early childhood, no other clinical symptoms of pulmonary disease were observed in childhood/adolescence. However, based on the long-term follow-up of 1 study patient (child), there is a risk for restrictive lung disease development in adulthood.

The presence of macular cherry-red spot was noted in both visceral and neurovisceral chronic ASMD patients. This observation is noteworthy since it was believed that the presence of cherry-red spot is associated with a neurological phenotype.¹⁵

The gold standard in the diagnosis of ASMD was (and still is) a method based on measuring acid sphingomyelinase (ASM) activity in peripheral blood leukocytes followed by *SMPD1* gene sequencing. Recently, a DBS test is in common use, utilizing the same diagnostic protocol with addition of biomarkers (lyso-sphingolipids) assessment.⁹ In 2010, lyso-glucosylceramide (lyso-Gb1), a newly introduced biomarker, was expected to provide breakthrough into GD field.¹⁶ An alternative metabolic pathway favored in state of β -glucocerebrosidase deficiency has been identified, where loads of Gb1 undergo deacylation due to an acid ceramidase activity, producing glucosylsphingosine (lyso-Gb1). The quantification of a de-acylated form of sphingomyelin (lyso-SM) and its carboxylated counterpart (lyso-SM-509) has been shown extremely useful in the diagnosis and monitoring of patients with ASMD and Niemann–Pick disease type C (NPC).^{17–19} The combined determination of both, lyso-SM and lyso-SM509 allowed the discrimination of ASMD from NPC, as ASMD patients having elevated levels mainly of lyso-SM, while both ASMD and NPC patients exhibit elevated levels of lysoSM-509.²⁰ However, some adults with attenuated chronic ASMD could present with normal lyso-SM but elevated lyso-SM509 (personal observation). Thus, both these biomarkers should be routinely used as a screening method for ASMD. Unfortunately, lyso-SM509 analysis is not available in Poland, while lyso-SM analysis has been used routinely for about 1 year. Despite the small number of patients and multiple assessments of lyso-SM, there is a noticeable difference between chronic visceral and neurovisceral ASMD patients, with the latter having higher lyso-SM levels.

Increased levels of ChT activity have been reported in several LSD, especially high for GD, due to macrophage activation.^{21–23} Mildly elevated ChT activity could be observed in chronic ASMD patients, as presented in our study. This biomarker should not be forgotten due to novel biomarkers development, especially lyso-SM.

The method of collecting and assessing ChT activity is relatively simple and remained the same for over

20 years, which guarantees comparability of results between years.²³ For these reasons, it is justly considered as a useful tool for clinical practice and management of GD patients and probably for ASMD.

Limitations

The study was limited by its retrospective nature and a relatively small number of patients, but given the rarity of ASMD, the paper is important in the field of inherited metabolic diseases.

Conclusions

1. Chronic ASMD is a slowly progressive disease.
2. Pediatric ASMD is characterized by spleno-hepatomegaly, dyslipidemia (with decreased HDL cholesterol as the most characteristic) and infiltrative (interstitial) lung disease. Both visceral and neurovisceral chronic ASMD patients may present with cherry-red spot.
3. Both acid sphingomyelinase activity and lyso-SM concentration in DBS should be regarded as a first-tier screening method for ASMD.




Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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References

1. Schuchman EH, Desnick RJ. Types A and B Niemann–Pick disease. *Mol Genet Metab*. 2017;120(1–2):27–33. doi:10.1016/j.jymgme.2016.12.008
2. Geberhiwot T, Wasserstein M, Wanninayake S, et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann–Pick disease types A, B and A/B). *Orphanet J Rare Dis*. 2023;18(1):85. doi:10.1186/s13023-023-02686-6
3. McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). *Orphanet J Rare Dis*. 2017;12(1):41. doi:10.1186/s13023-017-0572-x
4. Pavlů-Pereira H, Asfaw B, Poupčtová H, et al. Acid sphingomyelinase deficiency. Phenotype variability with prevalence of intermediate phenotype in a series of twenty-five Czech and Slovak patients: A multi-approach study. *J Inher Metab Dis*. 2005;28(2):203–227. doi:10.1007/s10545-005-5671-5
5. Jones SA, McGovern M, Lidove O, et al. Clinical relevance of endpoints in clinical trials for acid sphingomyelinase deficiency enzyme replacement therapy. *Mol Genet Metab*. 2020;131(1–2):116–123. doi:10.1016/j.jymgme.2020.06.008

6. Lipiński P, Kuchar L, Zakharova EY, Baydakova GV, Ługowska A, Tylki-Szymańska A. Chronic visceral acid sphingomyelinase deficiency (Niemann–Pick disease type B) in 16 Polish patients: Long-term follow-up. *Orphanet J Rare Dis*. 2019;14(1):55. doi:10.1186/s13023-019-1029-1
7. Gal AE, Fash FJ. Synthesis of 2-N-(Hexadecanoyl)-amino-4-nitrophenyl phosphorylcholine-hydroxide, a chromogenic substrate for assaying sphingomyelinase activity. *Chem Phys Lipids*. 1976;16(1):71–79. doi:10.1016/0009-3084(76)90015-3
8. Hollak CE, Van Weely S, Van Oers MH, Aerts JM. Marked elevation of plasma chitotriosidase activity: A novel hallmark of Gaucher disease. *J Clin Invest*. 1994;93(3):1288–1292. doi:10.1172/JCI117084
9. Verma J, Thomas DC, Kasper DC, et al. Inherited metabolic disorders: Efficacy of enzyme assays on dried blood spots for the diagnosis of lysosomal storage disorders. *JMID Rep*. 2016;31:15–27. doi:10.1007/8904_2016_548
10. Ferreira CR, Rahman S, Keller M, Zschocke J; ICIMD Advisory Group. An International Classification of Inherited Metabolic Disorders (ICIMD). *J Inherit Metab Dis*. 2021;44(1):164–177. doi:10.1002/jimd.12348
11. Lipiński P, Tylki-Szymańska A. The liver and lysosomal storage diseases: From pathophysiology to clinical presentation, diagnostics, and treatment. *Diagnostics (Basel)*. 2024;14(12):1299. doi:10.3390/diagnostics14121299
12. Wasserstein M, Dionisi-Vici C, Giugliani R, et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). *Mol Genet Metab*. 2019;126(2):98–105. doi:10.1016/j.ymgme.2018.11.014
13. Lipiński P, Ługowska A, Zakharova EY, Socha P, Tylki-Szymańska A. Diagnostic algorithm for cholesteryl ester storage disease: Clinical presentation in 19 Polish patients. *J Pediatr Gastroenterol Nutr*. 2018;67(4):452–457. doi:10.1097/MPG.0000000000002084
14. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18(2):441. doi:10.3390/ijms18020441
15. Chen H, Chan AY, Stone DU, Mandal NA. Beyond the cherry-red spot: Ocular manifestations of sphingolipid-mediated neurodegenerative and inflammatory disorders. *Surv Ophthalmol*. 2014;59(1):64–76. doi:10.1016/j.survophthal.2013.02.005
16. Daykin EC, Ryan E, Sidransky E. Diagnosing neuronopathic Gaucher disease: New considerations and challenges in assigning Gaucher phenotypes. *Mol Genet Metab*. 2021;132(2):49–58. doi:10.1016/j.ymgme.2021.01.002
17. Polo G, Burlina AP, Kolamunnage TB, et al. Diagnosis of sphingolipidoses: A new simultaneous measurement of lysosphingolipids by LC-MS/MS. *Clin Chem Lab Med*. 2017;55(3):403–414. doi:10.1515/cclm-2016-0340
18. Piraud M, Pettazzoni M, Lavoie P, et al. Contribution of tandem mass spectrometry to the diagnosis of lysosomal storage disorders. *J Inherit Metab Dis*. 2018;41(3):457–477. doi:10.1007/s10545-017-0126-3
19. Voorink-Moret M, Goorden SMI, Van Kuilenburg ABP, et al. Rapid screening for lipid storage disorders using biochemical markers: Expert center data and review of the literature. *Mol Genet Metab*. 2018;123(2):76–84. doi:10.1016/j.ymgme.2017.12.431
20. Kubaski F, Burlina A, Pereira D, et al. Quantification of lysosphingomyelin and lysosphingomyelin-509 for the screening of acid sphingomyelinase deficiency. *Orphanet J Rare Dis*. 2022;17(1):407. doi:10.1186/s13023-022-02560-x
21. Kadali S, Koluasu A, Sunkara S, Gummadi MR, Undamatla J. Clinical evaluation of chitotriosidase enzyme activity in Gaucher and Niemann–Pick A/B diseases: A retrospective study from India. *Clin Chim Acta*. 2016;457:8–11. doi:10.1016/j.cca.2016.03.004
22. Szymańska-Rożek P, Czartoryska B, Kleinotiene G, Lipiński P, Tylki-Szymańska A, Ługowska A. A 20-year longitudinal study of plasma chitotriosidase activity in treated Gaucher disease type 1 and 3 patients: A qualitative and quantitative approach. *Biomolecules*. 2023;13(3):436. doi:10.3390/biom13030436
23. Tylki-Szymańska A, Szymańska-Rożek P, Hasiński P, Ługowska A. Plasma chitotriosidase activity versus plasma glucosylsphingosine in wide spectrum of Gaucher disease phenotypes: A statistical insight. *Mol Genet Metab*. 2018;123(4):495–500. doi:10.1016/j.ymgme.2018.02.004