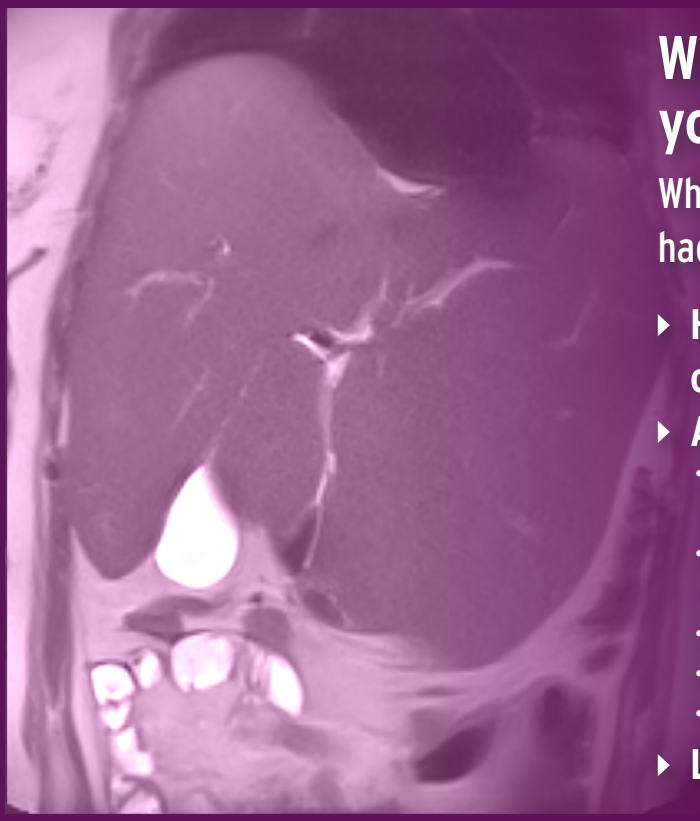
Hepatosplenomegaly in a Lean Patient. Apparent Fatty Liver Disease



What's in your differential?

What would you expect if you had a patient exhibiting:

- **Hepatomegaly without cholestasis**
- **Abnormal liver enzymes**
  - Elevated transaminases (AST: 51 U/L, ALT: 44 U/L)
  - Elevated kPa without elevated BMI
  - Elevated GGT (26 U/L)
  - Elevated bilirubin levels
  - Elevated alkaline phosphatase
- **Low HDL-C (15 mg/dL)**

It's not what you think...

Hepatologists and pediatric gastroenterologists can play a critical role in the early diagnosis of ASMD

ASMD, historically known as Niemann-Pick disease types A, A/B, and B, is a progressive and often life-threatening genetic disease.[1]

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMI=body mass index; GGT=gamma-glutamyl transferase; HDL-C=high-density lipoprotein cholesterol; kPa=kilopascal.

SANOFI GENZYME

ASMD
ACID SPHINGOMYELINASE DEFICIENCY

HEPATOLOGISTS AND PEDIATRIC GASTROENTEROLOGISTS ARE ON THE FOREFRONT OF DIAGNOSING ASMD

Cryptogenic liver disease? Multisystemic involvement? It could be ASMD

- **ASMD, caused by a deficiency in the enzyme acid sphingomyelinase (ASM),** is a progressive, multisystemic genetic disease that can lead to shortened life span in both children and adults[1,2]
- **ASMD symptoms can impact the lungs, liver, and spleen, as well as the hematologic system. Some types of ASMD can also affect the neurological system[1,2]**
- **The 3 subtypes of ASMD, type A, type A/B, and type B, have variable onset, presentation, and impacts on life expectancy. Regardless of type, ASMD can lead to lifelong multisystemic complications and uncertainty for patients[2]**

Identify signs and symptoms to enable early diagnosis

Percentage of patients who experience hallmark signs and symptoms of ASMD[1,3]*

Splenomegaly	Hepatomegaly	Interstitial lung disease	Thrombocytopenia	Gastrointestinal issues†
>90%	>70%	>80%	>50%	>75%

*Symptom prevalence data for splenomegaly, hepatomegaly, interstitial lung disease, and thrombocytopenia are only for patients with ASMD type B.

†Symptom prevalence data for gastrointestinal issues are for patients with all ASMD types.

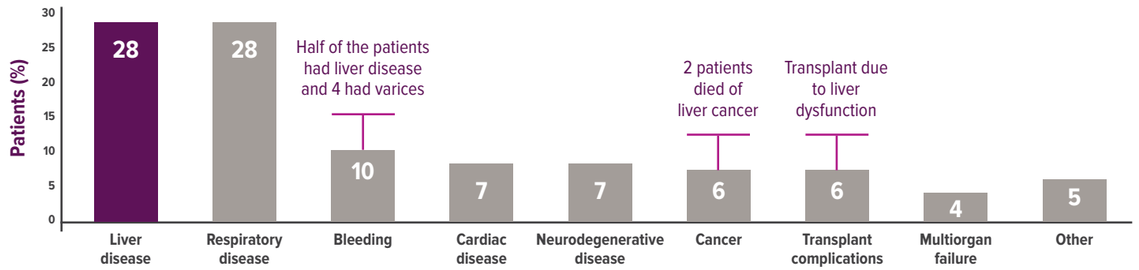
Hepatologists and pediatric gastroenterologists can play a key role in suspecting and diagnosing ASMD: **Early diagnosis is imperative for initiating symptom management and family screening[2]**

LIVER DISEASE: A LEADING CAUSE OF DEATH IN ASMD[4]

Patients with ASMD can experience significant morbidity and early mortality[5]

By age 35, ASMD type B patients have **~30% reduced survival probability** compared to the general US population‡

Primary causes of death in patients with ASMD types A/B and B[4]



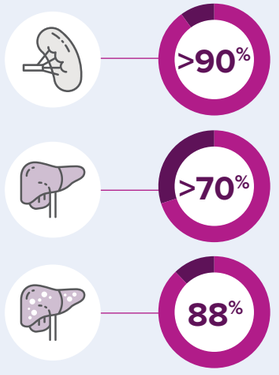
Cassiman D, et al. *Mol Genet Metab.* 2016;118(3):206-213.

Liver disease was also a common comorbidity in patients whose primary causes of death were listed as respiratory, cardiac, or multiorgan failure[4]

Based on a retrospective global study of 85 patients with ASMD that evaluated the causes of death and disease-related morbidity among patients with ASMD types A/B (n=27) and B (n=58). Data for 85 patients who died (n=78) or received liver transplant (n=7) were collected by treating physicians (n=27) or abstracted from previously published case studies (n=58).[4]

Know the hepatic signs

Splenomegaly, hepatomegaly, and liver fibrosis are hallmark signs of ASMD§



ASMD patients experience splenomegaly[1]

ASMD patients experience hepatomegaly resulting from infiltration of foamy cells into hepatic sinusoidal spaces, identified through abdominal examination and MRI. **Patients often present with liver volume >1.5x normal[1,6,7]**

Progressive liver fibrosis and liver dysfunction. In ASMD, these can occur when sphingomyelin accumulates in macrophages, Kupffer cells, and hepatocytes, transforming them into clusters of foamy cells[1,6]

ASMD patients may be at risk of cirrhosis, portal hypertension, and variceal bleeding[1,2,4]

Patients may also present with additional hepatic signs and symptoms, including[1,2]:

- **Abnormal liver chemistry tests**
- **Cryptogenic cirrhosis**
- Dyslipidemia
  - Elevated total cholesterol
  - Elevated LDL-C
  - Low HDL-C
  - Elevated VLDL-C
  - Elevated triglycerides

‡Data extrapolated from a Kaplan-Meier curve generated in an 11-year natural history study that evaluated morbidity and mortality in 59 patients with ASMD type B. At entry, 30 patients were in the pediatric age group (<18 years of age) and 29 patients were adults (≥18 years of age). There were 9 deaths during the follow-up period. Reduction in survival probability is absolute, not relative. US general population as of 2017.[5]

LDL-C=low-density lipoprotein cholesterol; MRI=magnetic resonance imaging; VLDL-C=very low-density lipoprotein cholesterol.

ASMD SIGNS AND SYMPTOMS OFTEN OVERLAP WITH OTHER LIVER DISEASES

ASMD patients can experience diagnostic delays of ~5 YEARS[7]

Phenotypic overlap with other hepatic conditions often leads to diagnostic delays[2]

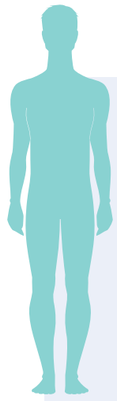
Hepatic manifestations of ASMD may mimic[2]:

- Nonalcoholic fatty liver disease (NAFLD)
- Autoimmune hepatic disease
- Chronic hepatitis B
- Cryptogenic cirrhosis
- Lysosomal acid lipase deficiency

Consider ASMD in patients presenting with liver abnormalities including:

In pediatric patients:

- Both dyslipidemia and abnormal LFTs[7]
- Hepatosplenomegaly without cholestasis or obesity[2]
- Apparent fatty liver disease and elevated liver enzymes without obesity[2]



In adult patients:

- Cryptogenic liver disease with splenomegaly[2]
- Fatty liver disease (NASH, NAFLD) with abnormal lipid profiles[2]

Early detection is the first step to prompt diagnosis and symptom management[2]

LFT=liver function test; NASH=nonalcoholic steatohepatitis.

UNEXPLAINED HEPATOSPLENOMEGALY? IT COULD BE ASMD. TEST TO KNOW

Missed diagnoses are common[2]

ASMD also shares the signs of other, more commonly seen multisystemic conditions

Because of the multisystemic nature of ASMD, it is also confused with other conditions including[1,2,8-10]:

- Acute lymphoblastic leukemia
- Non-Hodgkin lymphoma
- Congestive heart failure
- Cystic fibrosis
- Interstitial lung disease
- Other storage disorders

Know the signs and symptoms

Gaucher disease—another rare lysosomal storage disorder—shares significant phenotypic overlap with ASMD. Similar to ASMD, Gaucher disease is characterized by multisystemic and progressive symptoms that vary in onset and presentation.[1,10]

Among patients suspected of having Gaucher disease, an ASMD diagnosis is not uncommon[11]

Include ASMD and Gaucher disease in your differential diagnosis and parallel test[2]

IN ASMD, SPLENOMEGALY AND HEPATOMEGALY OFTEN PRESENT FIRST

A diagnostic approach for ASMD based on expert guidelines[2]

Splenomegaly +/- hepatomegaly

↓

1 or more features suggestive of ASMD:

Infants and children	After childhood
• Interstitial lung disease	• Interstitial lung disease
• Thrombocytopenia	• Thrombocytopenia
• Cherry-red maculae	• Low HDL-C
• Developmental delay	• Pathologic fractures
• Hypotonia	
• Low HDL-C	

NO →

Rule out other causes:

- **Gaucher disease**
- Infection
- Malignancy
- Liver disease
- Congestive heart failure
- Hematologic disease

↓ **YES**

↓

Test for ASMD

← **YES**

Guidelines recommend parallel testing for ASMD and Gaucher disease due to overlap of clinical manifestations[2,10]*

ASMD	Gaucher disease
ASM biochemical enzyme assay	ß-glucosidase biochemical enzyme assay

*Guidelines are based on a consensus of opinions from an international group of experts in ASMD.

TAKE THE STEP TOWARD AN ACCURATE DIAGNOSIS

Suspect ASMD? Diagnostic testing is simple[2]

Perform an ASM biochemical enzyme assay on isolated peripheral blood leukocytes, dried blood spots (DBS), or skin fibroblasts†

↓

Low residual ASM activity

↓

ASMD diagnosis confirmed

†Limitations of DBS testing include the potential effects of anemia and recent transfusions on results. Skin fibroblasts or *SMPD1* gene sequencing can be used in equivocal cases.

APRIL
Living with ASMD type B

Additional diagnostic confirmation can be achieved using molecular genetic testing[2]

An accurate ASMD diagnosis can enable early symptom management efforts from a multidisciplinary care team before disease progression becomes severe[2]

Cryptogenic liver disease? Abnormal liver enzymes? Hepatosplenomegaly?

IT COULD BE ASMD

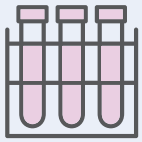
ASMD, historically known as Niemann-Pick disease types A, A/B, and B, is a multisystemic disease marked by liver dysfunction that can lead to significant morbidity and early mortality[1]

Hepatologists and pediatric gastroenterologists can make a difference

- Liver disease is a leading cause of mortality in ASMD[4]
- Know the hallmark signs and symptoms of ASMD that affect both children and adults[1]
  - Hepatomegaly
  - Splenomegaly
  - Interstitial lung disease
  - Thrombocytopenia

Include ASMD and Gaucher disease in your differential to enable early diagnosis and symptom management

- Guidelines recommend **parallel testing** for ASMD and Gaucher disease due to overlap of clinical manifestations[2,10]



SUSPECT ASMD? TEST TO KNOW

Diagnostic testing is simple—confirm a diagnosis of ASMD with an ASM biochemical enzyme assay[2]

Find more information on ASMD and testing at **ASMDfacts.com/HCP**

References: 1. McGovern MM, Avetisyan R, Sanson B-J, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). *Orphanet J Rare Dis.* 2017;12(1):41. **2.** McGovern MM, Dionisi-Vici C, Giugliani R, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. *Genet Med.* 2017;19(9):967-974. **3.** Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of illness in acid sphingomyelinase deficiency: a retrospective chart review of 100 patients. *JIMD Rep.* 2018;41:119-129. **4.** Cassiman D, Packman S, Bembi B, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): literature review and report of new cases. *Mol Genet Metab.* 2016;118:206-213. **5.** Data on file. Sanofi Genzyme. **6.** Thurberg BL, Wasserstein MP, Schiano T, et al. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). *Am J Surg Pathol.* 2012;36(8):1234-1246. **7.** McGovern MM, Wasserstein MP, Giugliani R, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics.* 2008;122:e341-e349. **8.** Leukemia & Lymphoma Society. Acute lymphoblastic leukemia signs and symptoms. Accessed December 16, 2021. https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/signs-and-symptoms **9.** Leukemia & Lymphoma Society. Non-Hodgkin lymphoma signs and symptoms. Accessed December 16, 2021. https://www.lls.org/lymphoma/non-hodgkin-lymphoma/signs-and-symptoms **10.** Mistry PK, Cappellini MD, Lukina E, et al. A reappraisal of Gaucher disease—diagnosis and management algorithms. *Am J Hematol.* 2011;86(1):110-115. **11.** Oliva P, Mechtler TP, Schwarz M, et al. Differential diagnosis of Niemann-Pick A/B disease (ASMD) in cases of suspected Gaucher disease. Poster presented at: 17th Annual WORLDSymposium; February 8-12 2021; San Diego, CA; Poster 305.

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MAT-US-2108628-v1.0-01/2022