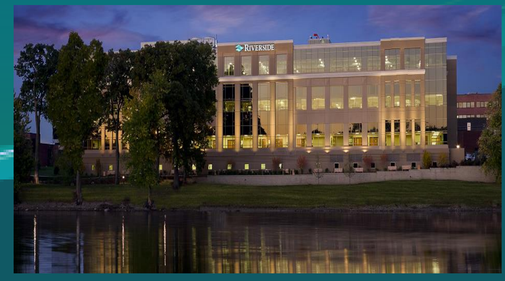
Psychosis and Sphingomyelinase: A Case Report on the Psychiatric Manifestations of Neimann-Pick Disease

Breanna Wennberg MD, Mohammad Farooqi DO, Kevin Varghese DO
Riverside Medical Center, Kankakee, Illinois



Background

Acid sphingomyelinase deficiency (ASMD), historically known as Neimann-Pick Disease (NPD), is a group of rare genetic, lysosomal storage disorders. Types A, B, and A/B, are caused by genetic mutations in the sphingomyelin phosphodiesterase A (SMPD1) gene and affect 1 in 250,000 individuals [1]. Type A, an infantile neurovisceral form with very low ASM activity is often fatal before the age of three due to severe neurological involvement. A less severe form, Type B, is characterized by a range of visceral symptoms and minimal neurological involvement. Historically, type C has been known to carry psychiatric manifestations but more recent research raises concern for psychiatric manifestations in an intermediate form, type A/B [3,4]. Interestingly, recent literature [2] demonstrates an association of the variance in SMPD1 gene with the pathophysiology of schizophrenia.

Case Presentation

We describe the case of a 26 year old male with no known past psychiatric history or family history who presented with erratic behavioral changes and paranoia. He received routine medical workup and was noted to have a past medical history of Neimann-Pick Disease Type B and two recent traumatic brain injuries due to dirt bike and car accidents. He has history of thrombocytopenia, hepatosplenomegaly, and pulmonary infiltrates related to Neimann-Pick Disease. Upon presentation, patient was internally preoccupied, disorganized, paranoid, and delusional which is atypical for ASMD. He was also noted to have ideas of reference and very poor sleep for multiple days. CT brain was negative for acute processes. The patient was diagnosed with brief psychotic disorder with concern for future development of schizophrenia. After establishing tolerance of oral Risperidone, an anti-psychotic, he was ultimately treated with Uzedy, a long acting injectable form of Risperidone for psychosis and mood stabilization.

Disclosure Information

Nothing to disclose

• An intermediate form, type A/B, has been noted more recently and encompasses symptoms of Type B with neurological involvement, extra-pyramidal and cerebellar signs, nystagmus, mental retardation, and psychiatric disorders which occur later in development when compared to Type A [6].

• Diagnosis can be difficult as molecular genetics studies can show alterations in SMPD1 genes which confirms ASMD type A or B but symptomatic overlap can lead to a diagnosis of A/B [8].

• There is very limited research regarding the intermediate form of ASMD type A/B, but one study demonstrates psychosocial effects of social isolation, peer rejection, chronic pain, fatigue, and living with a life-threatening disease which accompanied elevated stress levels and mood symptoms. In children with type A, increased signs of irritability, prolonged crying and sleep disturbance can be seen along with depression and psychosis requiring anti-depressant/psychotic therapies occurring in adult patients with ASMD [3].

• An analysis of human gene polymorphisms and brain gene expression in schizophrenia patients identified an association of SMPD1 and SMPD3 genes coding for acid- (ASM) and neutral sphingomyelinase-2 (NSM) [2].

• Excess sphingomyelin disrupts lysosomal function, leading to the accumulation of inflammatory lipids such as ceramides [7]. Research on brain lipid composition revealed that ceramide levels were increased in the prefrontal cortex white matter of post-mortem samples from both schizophrenic and bipolar patients. This finding suggests a potential association between ceramide accumulation and neuropsychiatric symptoms in these conditions [5].

Conclusions

Our patient raises concern for further diagnostic clarity with consideration for ASMD type A/B due to historical symptoms and current psychiatric presentation which was complicated by TBIs. There is minimal research on psychosis in patients with type A/B and thus lacks further investigations in treatment. There are potential associations between sphingolipid accumulation due to SMPD1 gene mutations and development of neuropsychiatric symptoms which can provide further clarity to those who develop psychosis and have history of ASMD.

References

[1] Bajwa H, Azhar W. Niemann-Pick Disease. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK556129/

[2] Chestnykh, D., Mühle, C., Schumacher, F., Kalinichenko, L. S., Löber, S., Gmeiner, P., Alzheimer, C., von Hörsten, S., Kleuser, B., Uebe, S., Ekici, A. B., Gulbins, E., Kornhuber, J., Jin, H. K., Bae, J. S., Lourdusamy, A., & Müller, C. P. (2025). Acid sphingomyelinase activity suggests a new antipsychotic pharmaco-treatment strategy for schizophrenia. *Molecular psychiatry*, 10.1038/s41380-025-02893-6. Advance online publication. https://doi.org/10.1038/s41380-025-02893-6

[3] 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* 18, 85 (2023). https://doi.org/10.1186/s13023-023-02686-6

[4] McGovern, M.M., Avetisyan, R., Sanson, BJ. *et al.* Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). *Orphanet J Rare Dis* 12, 41 (2017). https://doi.org/10.1186/s13023-017-0572-x .

[5] Smesny, S., Schmelzer, C. E. H., Hinder, A., Köhler, A., Schneider, C., Rudzok, M., Schmidt, U., Milleit, B., Milleit, C., Nenadic, I., Sauer, H., Neubert, R. H. H., & Fluhr, J. W. (2012). Skin Ceramide Alterations in First-Episode Schizophrenia Indicate Abnormal Sphingolipid Metabolism. *Schizophrenia Bulletin*, *39*(4), 933–941.

[6] Tirelli, C., Rondinone, O., Italia, M., Mira, S., Belmonte, L. A., De Grassi, M., Guido, G., Maggioni, S., Mondoni, M., Miozzo, M. R., & Centanni, S. (2024). The Genetic Basis, Lung Involvement, and Therapeutic Options in Niemann–Pick Disease: A Comprehensive Review. *Biomolecules*, *14*(2), 211. https://doi.org/10.3390/biom14020211

[7] Van Kruining, D., Luo, Q., van Echten-Deckert, G., Mielke, M. M., Bowman, A., Ellis, S., Oliveira, T. G., & Martinez-Martinez, P. (2020). Sphingolipids as prognostic biomarkers of neurodegeneration, neuroinflammation, and psychiatric diseases and their emerging role in lipidomic investigation methods. *Advanced Drug Delivery Reviews*, *159*, 232–244.

[8] Vélez Pinos, P. J., Saavedra Palacios, M. S., Colina Arteaga, P. A., & Arevalo Cordova, T. D. (2023). Niemann-Pick Disease: A Case Report and Literature Review. Cureus, 15(1), e33534. https://doi.org/10.7759/cureus.33534