WDOWIAK, Krystian, MACIOCHA, Agnieszka, WĄŻ, Julia, WITAS, Aleksandra, DROGOŃ, Justyna, CHACHAJ, Weronika, SZYMKOWIAK, Natalia and GARDOCKA, Ewa. N-acetylglutamate synthetase deficiency - literature review. Journal of Education, Health and Sport. 2025;77:56888. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.77.56888
https://apcz.umk.pl/JEHS/article/view/56888

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 10.12.2024. Revised: 12.01.2025. Accepted: 12.01.2025. Published: 13.01.2025.

N-acetylglutamate synthetase deficiency - literature review

Krystian Wdowiak[1*], Agnieszka Maciocha[2], Julia Wąż[3], Aleksandra Witas[1], Justyna Drogoń[1], Weronika Chachaj[1], Natalia Szymkowiak[2], Ewa Gardocka[4]

[1] Faculty of Medicine, Medical University of Lublin, Lublin, Aleje Racławickie 1, 20-059 Lublin, Poland
[2] Faculty of Dentistry, Medical University of Lublin, Lublin, Aleje Racławickie 1, 20-059 Lublin, Poland
[3] Faculty of Medicine, Wroclaw Medical University, Wroclaw, wybrzeże Ludwika Pasteura 1, 50-367 Wrocław, Poland
[4] Faculty of Dentistry, Wroclaw Medical University, Wroclaw, wybrzeże Ludwika Pasteura 1, 50-367 Wrocław, Poland

Krystian Wdowiak [K.W.]: krystianrrwdowiak@gmail.com;
ORCID: https://orcid.org/0000-0001-6579-3695

Agnieszka Maciocha [A.M.]: maciochaaga8@gmail.com;
ORCID: https://orcid.org/0009-0008-3752-332X

Julia Wąż [J.W.]: julia.waz02@gmail.com;
ORCID: https://orcid.org/0009-0000-2626-538X

Aleksandra Witas [A.W.]: aksandra.w@gmail.com;
ORCID: https://orcid.org/0000-0002-4082-2653

Justyna Drogoń [J.D.]: justyna123456789101112@gmail.com;
ORCID: https://orcid.org/0000-0002-3848-2186

Weronika Chachaj [W.C.]: weronikachachaj9@o2.pl;
ORCID: https://orcid.org/0009-0005-6346-4878

Natalia Szymkowiak [N.S.]: nataliaszymkowiak4@gmail.com;
ORCID: https://orcid.org/0009-0007-9973-8089

Ewa Gardocka [E.G.]: e.gardocka04@gmail.com;
ORCID: https://orcid.org/0009-0005-2677-915X

*Correspondence: Krystian Wdowiak (krystianrrwdowiak@gmail.com)

N-acetylglutamate synthetase deficiency - literature review

Summary

Introduction and purpose: N-Acetylglutamate Synthetase Deficiency (NAGSD, #237310) is a rare urea cycle disorder, primarily caused by autosomal recessive genetic mutations. Most affected individuals are homozygous for the disease-causing allele. Symptoms typically appear in the neonatal period. The NAGS enzyme is essential for catalyzing the synthesis of N-acetylglutamate, an allosteric activator of carbamoylphosphate synthetase 1 (CPS1), crucial for the urea cycle. Key biochemical markers include elevated ammonia, glutamine, and alanine; decreased citrulline; and respiratory alkalosis. Hyperammonemia is the main clinical feature, manifesting as nausea, vomiting, cognitive impairment, seizures, and, in severe cases, coma or death. Genetic testing remains the cornerstone of diagnosis, enabling identification of specific mutations. Treatment involves carbamylglutamate, an NAG analog that activates CPS1. The aim of this publication is to discuss various aspects of N-acetylglutamate synthetase deficiency based on the latest literature.

Material and methods: The PubMed database was searched to find scientific articles in which the terms "N-acetylglutamate synthetase," "NAGS deficiency," or "N-acetylglutamate synthetase deficiency" appear in the title, abstract, or keywords.

Conclusions: Expanding research aims to explore novel treatments, dietary strategies, and the safety of current therapies during pregnancy.

Key words: N-acetylglutamate synthetase, NAGS deficiency, N-acetylglutamate synthetase deficiency

Introduction

N-Acetylglutamate Synthetase Deficiency (NAGSD, #237310) is an extremely rare genetic disorder of the urea cycle (UCD) [1,2]. Among all UCDs, NAGSD is the least common and was first described in 1981 [1]. NAGS is a mitochondrial enzyme responsible for synthesizing N-acetylglutamate, an allosteric activator of carbamoylphosphate synthetase 1 (CPS1). Consequently, CPS1 deficiency and NAGSD are nearly indistinguishable in clinical and biochemical presentations [1,2,3]. However, differential diagnosis is crucial, as NAGSD is the only UCD currently amenable to effective treatment [4]. NAGSD can be classified as primary (genetically determined) or secondary (resulting from defects in organic and fatty acid metabolism) [4].

The primary biochemical feature of NAGSD is hyperammonemia, which manifests as a range of clinical symptoms, including nausea, vomiting, cognitive impairment, seizures, and, in severe cases, coma or death [1,2,4]. NAGSD is most commonly diagnosed in the early years of life. However, milder forms with partial NAGS activity have been reported in adults, with episodic headaches being the primary symptom [2].

Objective

This publication aims to provide an overview of various aspects of N-acetylglutamate synthetase deficiency based on the latest literature.

Methods

A PubMed search was conducted for scientific articles featuring the terms “N-acetylglutamate synthetase,” “NAGS deficiency,” or “N-acetylglutamate synthetase deficiency” in the title, abstract, or keywords. Articles discussing the etiology, epidemiology, symptomatology, diagnostics, and treatment of this disorder were selected. The search was limited to English-language articles published between 2015 and 2024 with free full-text access.

Etiology and pathophysiology

Ammonia is the primary toxic metabolite of nitrogen compounds in the human body. In the liver, it undergoes a series of metabolic transformations, converting into the less toxic urea (urea cycle) [5]. Urea cycle disorders (UCDs) lead to episodes of hyperammonemia, with varying severity and frequency depending on the specific enzyme deficiency and its extent [2]. Hyperammonemia can manifest with symptoms ranging from nausea, vomiting, and cognitive changes to seizures, coma, and death [1,2,4].

The human NAGS gene is located on chromosome 17 (17q21.31) and spans approximately 8.5 kb, comprising seven exons, six introns, a promoter, and an enhancer located about 3 kb upstream of the transcription start site [4,6]. The NAGS promoter regulates transcription through binding with specificity protein 1 (Sp1) and cAMP response element binding protein (CREB), while the enhancer interacts with hepatic nuclear factor 1 (HNF1) and nuclear factor Y (NF-Y), regulating liver-specific transcription of the gene [4].

Human NAGS is a mitochondrial enzyme structured into an N-terminal amino acid kinase (AAK) domain (residues 95–372) containing the L-arginine binding site and a C-terminal N-acetyltransferase (NAT) domain [7]. Its biological function is to catalyze the synthesis of N-acetylglutamate, an essential allosteric activator of carbamoylphosphate synthetase 1 (CPS1) [1]. As a result, the biochemical symptoms of NAGSD and CPS1 deficiency are identical, including elevated glutamine, reduced citrulline, normal orotic acid, and elevated ammonia [1].

Primary NAGSD is a genetically determined, autosomal recessive disorder [1,2,4]. Most affected individuals are homozygous for the disease-causing allele [8]. While the majority of NAGSD cases arise from mutations in coding or splicing regions, mutations in the enhancer region of the gene, which reduce its expression by impairing HNF1 binding, have also been

reported [4,8,9]. To date, approximately 50 mutations associated with NAGSD have been identified, over 60% of which are missense mutations [2].

Secondary NAGSD results from the administration of specific drugs or other metabolic disorders [4]. There have been cases of NAGSD induced by valproic acid treatment, where the drug metabolite (valproyl-CoA) inhibits NAGS activity [10,11]. Other disorders associated with secondary NAGSD include propionic acidemia (PA) and methylmalonic acidemia (MMA) [12,13]. Both conditions, inherited in an autosomal recessive manner, cause the accumulation of acyl-CoA, which inhibits NAGS activity [12,14].

Epidemiology

NAGSD is an extremely rare condition and the least common UCD [1]. Its estimated prevalence ranges from 1 in 2,000,000 to 1 in 7,000,000 live births [6,15]. Only around 100 cases of NAGSD have been reported in the literature to date [1].

Symptomatology

For many years, there was limited data regarding the typical age at which symptoms of N-Acetylglutamate Synthetase Deficiency (NAGSD) manifest [1]. A detailed analysis by Kenneson et al. [1] indicated that symptoms most commonly appear during the neonatal period, accounting for 58% of cases, while late-onset presentations are exceedingly rare, comprising only a few percent of cases [1]. The longest interval from birth to the onset of symptoms documented in the literature is 59 years [1].

Neonatal symptoms predominantly include poor feeding or feeding intolerance, vomiting, lethargy, hypertonia and/or hypotonia, seizures, and tachypnea [1]. In cases of later onset, symptoms typically involve vomiting, confusion or disorientation, ataxia, lethargy, decreased level of consciousness, seizures, and hypotonia [1]. An intriguing feature in some late-onset patients is a tendency to avoid protein-rich foods [1].

In certain individuals, the only symptom is recurrent headaches [2]. To date, three headache types associated with hyperammonemia have been described: migraine-associated cyclic vomiting syndrome, sporadic hemiplegic migraine, and tension-type headache [2,16]. The pathophysiology of these headaches remains poorly understood. It is hypothesized that they result from increased intracranial pressure due to intracellular glutamine accumulation, triggered by high ammonia levels [2]. Additionally, some researchers suggest that disrupted

arginine metabolism, a feature of certain UCDs, may impair nitric oxide (NO) synthesis. Reduced NO levels could hinder intracranial pressure regulation by limiting cerebral vasodilation [17].

Recently, a case was reported in which 3-methylglutaconic aciduria (3-MGA) was attributed to NAGSD [18]. The authors speculate that this reflects severe metabolic decompensation, proposing 3-MGA as a potential marker of severe NAGSD, although further studies are needed [18].

Common biochemical and clinical markers of NAGSD include elevated ammonia, elevated glutamine and alanine, decreased citrulline, normal (or occasionally reduced) orotic acid, and respiratory alkalosis [1].

Symptoms of NAGSD are frequently triggered by specific factors, including high-fever illnesses [4], high-protein meals [1], the introduction of cow's milk into the diet [1], insufficient food intake and dehydration [2], upper respiratory infections [1], traffic accidents [1], bone fractures [9], pregnancy, and the postpartum period [14].

Diagnostics

Due to the nearly identical clinical and biochemical presentations of N-Acetylglutamate Synthetase Deficiency (NAGSD) and carbamoylphosphate synthetase 1 (CPS1) deficiency, additional testing is essential to establish an accurate diagnosis [1].

Historically, measuring NAGS activity in liver biopsies was a common diagnostic procedure. However, NAGS activity levels were highly variable among patients, with some exhibiting normal enzyme activity despite the disease, and reduced levels being observed in healthy individuals [1]. This test was often combined with arginine stimulation testing [1].

Currently, genetic testing remains the gold standard for diagnosing NAGSD, enabling the identification of mutations characteristic of the disease [1,3]. Researchers have highlighted the need to expand genetic testing panels due to the discovery of novel mutations, including those in the enhancer region of the gene [4].

A widely used diagnostic approach is a therapeutic trial with carbamylglutamate, combined with ammonia level measurements. This method often confirms or excludes NAGSD in ambiguous cases [1]. However, there is debate regarding whether other treatments for

hyperammonemia should be discontinued during the trial [1,19]. It is important to note that clinical improvement after carbamylglutamate administration is not entirely specific to NAGSD, as it can also occur in some other urea cycle disorders (UCDs) [1,20].

Liquid chromatography-tandem mass spectrometry has been reported as a diagnostic tool for NAGSD in a single study, but its clinical utility requires further validation [21].

Newborn screening for UCDs is performed in some countries [1,22]. The rationale for these screenings lies in the poor prognosis associated with delayed treatment—10% of affected infants die within the first year, and 30% experience intellectual disability [23]. According to Vasquez-Loarte et al. [22], including UCDs in newborn screening could detect at least two-thirds of affected individuals.

In summary, many researchers recommend an optimized diagnostic strategy combining a therapeutic trial with carbamylglutamate and simultaneous genetic testing [1,3,24].

Treatment

Most urea cycle disorders (UCDs) are conventionally treated using ammonia-scavenging agents (e.g., sodium benzoate and sodium phenylacetate), arginine supplementation to enhance urea cycle efficiency, and hemodiafiltration [3,24].

N-Acetylglutamate Synthetase Deficiency (NAGSD) remains the only UCD with a specific treatment [1]. The standard therapy for NAGSD involves carbamylglutamate (a NAG analog that activates CPS1), administered in maintenance doses ranging from 15 to 320 mg/kg/day, as reported in the literature [1,25–28]. Currently, there are no definitive guidelines regarding dietary protein restriction during carbamylglutamate therapy. However, some researchers suggest further investigation is warranted, as neurological symptoms have been reported in patients consuming more than 3.5 g/kg of protein daily [1,29]. There is limited data on the safety of carbamylglutamate use during pregnancy and lactation. Animal studies in rats indicate potential adverse effects on fetal and neonatal growth and development, although no abnormalities have been reported in the limited human cases where pregnant or lactating women with NAGSD continued carbamylglutamate therapy [14].

When NAGSD arises during valproic acid therapy, it is crucial to determine whether the patient has an asymptomatic primary form of the disease [10]. In cases of secondary NAGSD, discontinuation of valproic acid is recommended where possible. If discontinuation is not

feasible, dose reduction or the addition of carbamylglutamate to the treatment regimen should be considered [10]. There is also emerging evidence suggesting carbamylglutamate may have a role in managing propionic acidemia (PA) and methylmalonic acidemia (MMA), although further studies are needed [12,13].

Although carbamylglutamate therapy is the gold standard for NAGSD, cases have been reported where treatment involved ammonia-scavenging agents combined with protein restriction, with or without arginine and/or citrulline supplementation [1,8]. These approaches have yielded varying outcomes, ranging from full recovery to the development of intellectual disabilities [1].

Liver transplantation has been reported in two cases of children with NAGSD. The success of this intervention appears to depend on the timing of the operation. A child who underwent transplantation at six weeks of age developed normally, while another child transplanted at eight months later experienced intellectual disability [1,30].

A study by Sonaimuthu et al. [31] suggests that NAGSD could potentially be treated using gene therapy. However, human studies are currently lacking, and further research is necessary to evaluate its clinical application.

Summary

N-Acetylglutamate Synthetase Deficiency (NAGSD, #237310) is an extremely rare urea cycle disorder, primarily of genetic origin. It manifests as a primary condition due to autosomal recessive inheritance, with most affected individuals being homozygous for the pathogenic allele. Secondary NAGSD arises from specific drug exposures or other metabolic disturbances. Symptoms of the disorder typically emerge during the neonatal period, accounting for 58% of cases.

The biological role of N-acetylglutamate synthetase (NAGS) is to catalyze the synthesis of N-acetylglutamate, a critical allosteric activator of carbamoylphosphate synthetase 1 (CPS1), an enzyme essential for the proper function of the urea cycle. Common biochemical and clinical markers of NAGSD include elevated ammonia, glutamine, and alanine; decreased citrulline; normal or occasionally reduced orotic acid; and respiratory alkalosis. The hallmark biochemical feature is hyperammonemia, which can lead to a range of clinical symptoms, including nausea, vomiting, cognitive changes, seizures, and, in severe cases, coma or death.

The diagnostic cornerstone for NAGSD is genetic testing, which identifies mutations characteristic of this disorder. Standard treatment involves the use of carbamylglutamate, an NAG analog that stimulates CPS1 activity and mitigates the effects of the enzymatic deficiency.

Despite its rarity, expanding research on NAGSD is warranted due to the limited number of studies available. Further investigations are necessary to confirm the safety of treatments such as carbamylglutamate during pregnancy and to explore novel therapies, including gene therapy. Preliminary mentions of carbamylglutamate's potential application in treating propionic acidemia (PA) and methylmalonic acidemia (MMA) also require validation. Moreover, examining the role of dietary modifications and specific amino acid supplementation could provide additional insights into managing the disorder effectively.

Author's contribution:

Conceptualization: K.W., A.M.; methodology: K.W., A.M.; software: K.W., A.M., J.W., A.W.; formal analysis: K.W., A.M., J.W., A.W.; investigation: K.W., A.M., J.W., A.W., J.D., W.C.; resources: K.W., A.M., J.W., A.W., N.S., E.G.; data curation: K.W., A.M., J.W., A.W., N.S., E.G.; writing - rough preparation: K.W., A.M., J.W., A.W., J.D., W.C., N.S., E.G.; writing - review and editing: K.W., A.M., J.W., A.W., J.D., W.C., N.S., E.G.; visualization:K.W., A.M., A.W.; supervision: K.W., A.M.; project administration: K.W., A.M. All authors have read and agreed to the published version of the manuscript.

Funding statement: This research received no external funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: Publicly available datasets were analyzed in this study. This data can be found here: https://pubmed.ncbi.nlm.nih.gov/ (access 2024.10.02).

Conflicts of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Kenneson A, Singh RH. Presentation and management of N-acetylglutamate synthase deficiency: a review of the literature. Orphanet J Rare Dis. 2020 Oct 9;15(1):279. doi: 10.1186/s13023-020-01560-z. PMID: 33036647; PMCID: PMC7545900.
2. Cavicchi C, Chilleri C, Fioravanti A, Ferri L, Ripandelli F, Costa C, Calabresi P, Prontera P, Pochiero F, Pasquini E, Funghini S, la Marca G, Donati MA, Morrone A. Late-Onset N-Acetylglutamate Synthase Deficiency: Report of a Paradigmatic Adult Case Presenting with Headaches and Review of the Literature. Int J Mol Sci. 2018 Jan 24;19(2):345. doi: 10.3390/ijms19020345. PMID: 29364180; PMCID: PMC5855567.
3. Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, Mandel H, Martinelli D, Pintos-Morell G, Santer R, Skouma A, Servais A, Tal G, Rubio V, Huemer M, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019 Nov;42(6):1192-1230. doi: 10.1002/jimd.12100. Epub 2019 May 15. PMID: 30982989.
4. Williams M, Burlina A, Rubert L, Polo G, Ruijter GJG, van den Born M, Rüfenacht V, Haskins N, van Zutven LJCM, Tuchman M, Saris JJ, Häberle J, Caldovic L. N-Acetylglutamate Synthase Deficiency Due to a Recurrent Sequence Variant in the N-acetylglutamate Synthase Enhancer Region. Sci Rep. 2018 Oct 18;8(1):15436. doi: 10.1038/s41598-018-33457-0. PMID: 30337552; PMCID: PMC6194121.
5. Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2017 Jun 22]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1217/
6. Summar ML, Koelker S, Freedenberg D, Le Mons C, Haberle J, Lee HS, Kirmse B; European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD). Electronic address: http://www.e-imd.org/en/index.phtml; Members of the Urea Cycle Disorders Consortium (UCDC). Electronic address: http://rarediseasesnetwork.epi.usf.edu/ucdc/. The incidence of urea cycle disorders. Mol Genet Metab. 2013 Sep-Oct;110(1-2):179-80. doi: 10.1016/j.ymgme.2013.07.008. Epub 2013 Jul 18. PMID: 23972786; PMCID: PMC4364413.

7. Shi D, Allewell NM, Tuchman M. The N-Acetylglutamate Synthase Family: Structures, Function and Mechanisms. Int J Mol Sci. 2015 Jun 9;16(6):13004-22. doi: 10.3390/ijms160613004. PMID: 26068232; PMCID: PMC4490483.
8. Sancho-Vaello E, Marco-Marín C, Gougeard N, Fernández-Murga L, Rüfenacht V, Mustedanagic M, Rubio V, Häberle J. Understanding N-Acetyl-L-Glutamate Synthase Deficiency: Mutational Spectrum, Impact of Clinical Mutations on Enzyme Functionality, and Structural Considerations. Hum Mutat. 2016 Jul;37(7):679-94. doi: 10.1002/humu.22995. Epub 2016 May 6. PMID: 27037498.
9. van de Logt AE, Kluijtmans LA, Huigen MC, Janssen MC. Hyperammonemia due to Adult-Onset N-Acetylglutamate Synthase Deficiency. JIMD Rep. 2017;31:95-99. doi: 10.1007/8904_2016_565. Epub 2016 May 5. PMID: 27147233; PMCID: PMC5272844.
10. Sattar Y, Wasiq S, Yasin W, Khan AM, Adnan M, Shrestha S, Patel NB, Latchana S. Carglumic Acid Treatment of a Patient with Recurrent Valproic Acid-induced Hyperammonemia: A Rare Case Report. Cureus. 2018 Sep 12;10(9):e3292. doi: 10.7759/cureus.3292. PMID: 30443462; PMCID: PMC6235635.
11. Tang JY, Kiang TKL, Ensom MHH. Pharmacokinetic Interactions between Valproic Acid and Lorazepam (PIVOtAL Study): A Review of Site-Specific Practices. Can J Hosp Pharm. 2017 May-Jun;70(3):171-178. doi: 10.4212/cjhp.v70i3.1656. Epub 2017 Jun 30. PMID: 28680170; PMCID: PMC5491192.
12. Nashabat M, Obaid A, Al Mutairi F, Saleh M, Elamin M, Ahmed H, Ababneh F, Eyaid W, Alswaid A, Alohali L, Faqeih E, Aljeraisy M, Hussein MA, Alasmari A, Alfadhel M. Evaluation of long-term effectiveness of the use of carglumic acid in patients with propionic acidemia (PA) or methylmalonic acidemia (MMA): study protocol for a randomized controlled trial. BMC Pediatr. 2019 Jun 13;19(1):195. doi: 10.1186/s12887-019-1571-y. PMID: 31196016; PMCID: PMC6563377.
13. Tummolo A, Melpignano L, Carella A, Di Mauro AM, Piccinno E, Vendemiale M, Ortolani F, Fedele S, Masciopinto M, Papadia F. Long-term continuous N-carbamylglutamate treatment in frequently decompensated propionic acidemia: a case report. J Med Case Rep. 2018 Apr 22;12(1):103. doi: 10.1186/s13256-018-1631-1. PMID: 29679984; PMCID: PMC5911373.
14. Abou Haidar L, Pachnis P, Gotway GK, Ni M, DeBerardinis RJ, McNutt MC. Partial N-acetyl glutamate synthase deficiency presenting as postpartum hyperammonemia: Diagnosis and subsequent pregnancy management. JIMD Rep. 2023 Sep 7;64(6):403-409. doi: 10.1002/jmd2.12388. PMID: 37927481; PMCID: PMC10623101.

15. Peoc'h K, Damaj L, Pelletier R, Lefèvre C, Dubourg C, Denis MC, Bendavid C, Odent S, Moreau C. Early care of N-acetyl glutamate synthase (NAGS) deficiency in three infants from an inbred family. Mol Genet Metab Rep. 2020 Jan 24;22:100558. doi: 10.1016/j.ymgmr.2019.100558. PMID: 32021803; PMCID: PMC6994713.
16. Gelfand AA, Gallagher RC. Cyclic vomiting syndrome versus inborn errors of metabolism: A review with clinical recommendations. Headache. 2016 Jan;56(1):215-21. doi: 10.1111/head.12749. Epub 2015 Dec 18. PMID: 26678622; PMCID: PMC4728152.
17. Nagasaka H, Yorifuji T, Egawa H, Inui A, Fujisawa T, Komatsu H, Tsukahara H, Uemoto S, Inomata Y. Characteristics of NO cycle coupling with urea cycle in non-hyperammonemic carriers of ornithine transcarbamylase deficiency. Mol Genet Metab. 2013 Jul;109(3):251-4. doi: 10.1016/j.ymgme.2013.04.013. Epub 2013 Apr 28. PMID: 23669167.
18. Selvanathan A, Demetriou K, Lynch M, Lipke M, Bursle C, Elliott A, Inwood A, Foyn L, McWhinney B, Coman D, McGill J. N-acetylglutamate synthase deficiency with associated 3-methylglutaconic aciduria: A case report. JIMD Rep. 2022 Jul 22;63(5):420-424. doi: 10.1002/jmd2.12318. PMID: 36101823; PMCID: PMC9458610.
19. Van Leynseele A, Jansen A, Goyens P, Martens G, Peeters S, Jonckheere A, De Meirleir L. Early treatment of a child with NAGS deficiency using N-carbamyl glutamate results in a normal neurological outcome. Eur J Pediatr. 2014 Dec;173(12):1635-8. doi: 10.1007/s00431-013-2205-2. PMID: 24233332.
20. Sugiyama Y, Shimura M, Ogawa-Tominaga M, Ebihara T, Kinouchi Y, Isozaki K, Matsuhashi T, Tajika M, Fushimi T, Ichimoto K, Matsunaga A, Ishida T, Mizutani K, Tsuruoka T, Murayama K. Therapeutic effect of N-carbamylglutamate in CPS1 deficiency. Mol Genet Metab Rep. 2020 Jul 8;24:100622. doi: 10.1016/j.ymgmr.2020.100622. PMID: 32670798; PMCID: PMC7347628.
21. McNutt, Markey C., et al. "DEFICIENCY OF N-ACETYLGLUTAMATE SYNTHASE (NAGS) PRESENTING AS POSTPARTUM HYPERAMMONEMIA." MOLECULAR GENETICS AND METABOLISM. Vol. 123. No. 3. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA: ACADEMIC PRESS INC ELSEVIER SCIENCE, 2018.
22. Vasquez-Loarte T, Thompson JD, Merritt JL 2nd. Considering Proximal Urea Cycle Disorders in Expanded Newborn Screening. Int J Neonatal Screen. 2020 Oct 8;6(4):77. doi: 10.3390/ijns6040077. PMID: 33124615; PMCID: PMC7712149.

23. Burgard P, Kölker S, Haege G, Lindner M, Hoffmann GF. Neonatal mortality and outcome at the end of the first year of life in early onset urea cycle disorders--review and meta-analysis of observational studies published over more than 35 years. J Inherit Metab Dis. 2016 Mar;39(2):219-29. doi: 10.1007/s10545-015-9901-1. Epub 2015 Dec 3. PMID: 26634836.
24. Reigstad H, Woldseth B, Häberle J. Normal Neurological Development During Infancy Despite Massive Hyperammonemia in Early Treated NAGS Deficiency. JIMD Rep. 2017;37:45-47. doi: 10.1007/8904_2017_13. Epub 2017 Mar 9. PMID: 28275973; PMCID: PMC5740051.
25. Ah Mew N, Caldovic L. N-acetylglutamate synthase deficiency: an insight into the genetics, epidemiology, pathophysiology, and treatment. Appl Clin Genet. 2011 Aug 24;4:127-35. doi: 10.2147/TACG.S12702. PMID: 23776373; PMCID: PMC3681184.
26. Recordati Rare Diseases. (2021) US Prescribing Information. https://www.recordatirarediseases.com/files/inline-files/carbaglu-pi-122019.pdf. (accessed 2024.10.02)
27. Recordati Rare Diseases. (2021) CARBAGLU® (Carglumic Acid) Tablets 200 mg Receives U.S. FDA Approval for a New Indication to Treat Acute Hyperammonemia Associated with Propionic Acidemia and Methylmalonic Acidemia. https://www.recordatirarediseases.com/us/node/218 (accessed 2024.10.02)
28. Alfadhel, M., Nashabat, M., Saleh, M., Elamin, M., Alfares, A., Al Othaim, A., Umair, M., Ahmed, H., Ababneh, F., Al Mutairi, F., Eyaid, W., Alswaid, A., Alohali, L., Faqeih, E., Almannai, M., Aljeraisy, M., Albdah, B., Hussein, M. A., Rahbeeni, Z., & Alasmari, A. (2021). Long-term effectiveness of carglumic acid in patients with propionic acidemia (PA) and methylmalonic acidemia (MMA): a randomized clinical trial. Orphanet journal of rare diseases, 16(1), 422. https://doi.org/10.1186/s13023-021-02032-8
29. Singh RH, Bourdages MH, Kurtz A, MacLoed E, Norman C, Ratko S, van Calcar SC, Kenneson A. The efficacy of Carbamylglutamate impacts the nutritional management of patients with N-Acetylglutamate synthase deficiency. Orphanet J Rare Dis. 2024 Apr 18;19(1):168. doi: 10.1186/s13023-024-03167-0. PMID: 38637895; PMCID: PMC11027358.
30. García Vega M, Andrade JD, Morais A, Frauca E, Muñoz Bartolo G, Lledín MD, Bergua A, Hierro L. Urea cycle disorders and indications for liver transplantation. Front

Pediatr. 2023 Mar 3;11:1103757. doi: 10.3389/fped.2023.1103757. PMID: 36937980; PMCID: PMC10020209.

31. Sonaimuthu P, Senkevitch E, Haskins N, Uapinyoying P, McNutt M, Morizono H, Tuchman M, Caldovic L. Gene delivery corrects N-acetylglutamate synthase deficiency and enables insights in the physiological impact of L-arginine activation of N-acetylglutamate synthase. Sci Rep. 2021 Feb 11;11(1):3580. doi: 10.1038/s41598-021-82994-8. PMID: 33574402; PMCID: PMC7878489.