EPH170

Is Hyperammonemic Crisis in Inborn Errors of Metabolism an Ultra-Orphan Disease? – A Literature Review

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Introduction

Hyperammonemic Crisis (HAC) in Inborn Errors of Metabolism (IEM) occurs in Urea Cycle Disorder (UCD) and Organic Aciduria Disorders (OAD). The prevalence of UCDs and OAs in United States and in 5 European countries is expected to provide a good estimate of HAC in IEM.

Objective

Hyperammonemic Crisis (HAC) is a serious acute condition that may lead to coma or death in patients with Urea Cycle Disorders (UCD) or Organic Aciduria Disorders (OAD). This review provides an overview of the incidence of HAC in UCD and OAD, beyond individual disease prevalence.

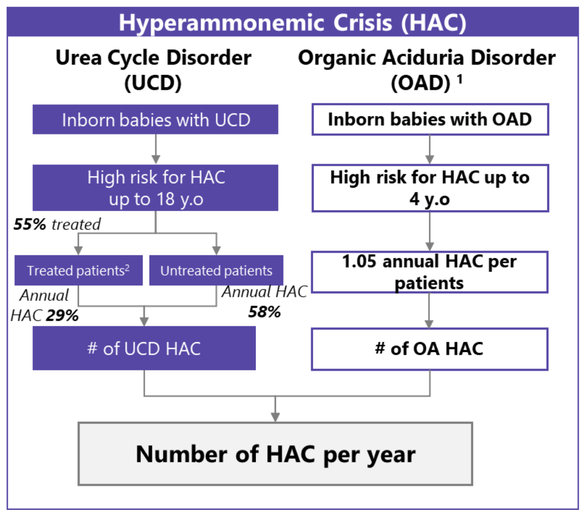
Methodology

A literature review conducted in Pubmed, Scopus, Embase, Medline, and GoogleScholar. Conference/research papers, medical/consortium guideline, information published by health technology assessment agencies, and manufacturer reports included. Only publications in English included. A mathematic multi-compartmental model used to calculate overall HAC in the US and 5 countries in Europe (UK, Germany, France, Italy, and Spain).

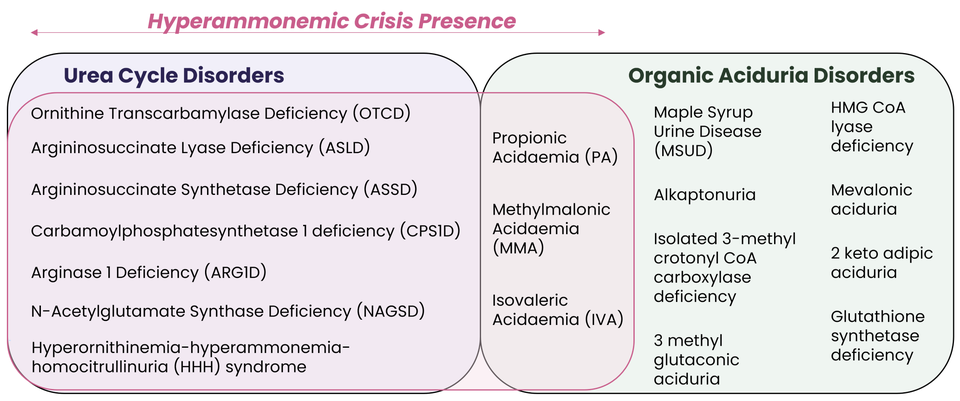
Results

21 publications in UCD, and 12 publications in OAD identified. The prevalence of UCD in the US is 1:35'000 and ranged from 1:34'622 to 1:63'095 in Europe. HAC in OAD only occurred in Propionic Acidemia (PA), Methylmalonic Acidemia (MMA), and Isovaleric Acidemia (IVA) with prevalence of 1:242'741 (PA), 1:69'354 (MMA), and 1:159'150 (IVA) in the US, and ranging from 1:105'082 to 1:202'617 (PA), 1:105'082 to 1:159'199 (MMA), and 1:155'000 (IVA) in Europe, respectively. HAC in UCD only occurred up to the age of 18 years, with an incidence of 0.58/ patient/ year for untreated patients, and an incidence of 0.28/patient/year for chronically treated patients (with glycerol phenylbutyrate and sodium phenylbutyrate). HAC in OAD occurred only up to the age of 4 years, with an incidence of 1.05/patient/year in an in-patient setting. The annual incidence of HAC within UCD and OAD patients estimated approximately 1'898 per year in 2021

NUMBER OF HYPERAMMONEMIC CRISIS PER YEAR



1 OAD with HAC are only: Propionic Acidaemia (PA), Methylmalonic Acidaemia (MMA), Isovaleric Acidaemia (IVA). Assessment in this deck only covers 3 OAD types mentioned.
2 Treated by Buphenyl and Ravicti



UREA CYCLE DISORDER (UCD)

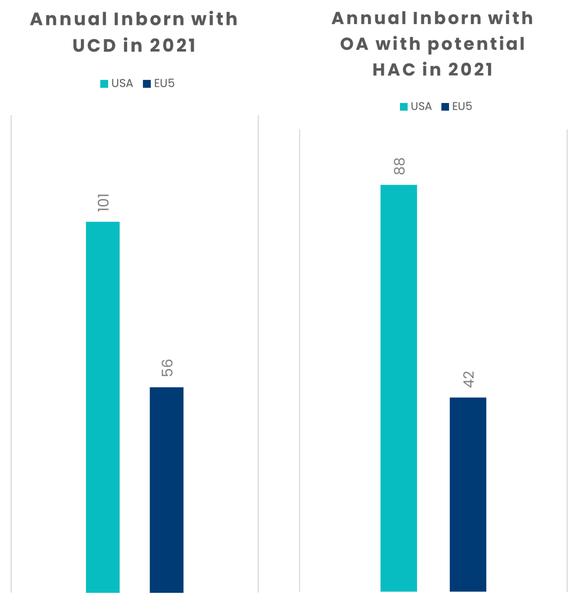
Variable	Estimates	Sources
Annual UCD inborn babies	157	Summar et al. (2013), Martin-Hernandez et al. (2014), Nettesheim et al. (2017)
Age range of HAC	0-18 y.o.	Batshaw et al. (2015)
Annual HAC occurrence	Treated: 28%[2] Untreated: 58%	Batshaw et al. (2015)
Ravicti and Buphenyl share from total UCD patients	55%	Acer therapeutics SEC 8-K (2020)

ORGANIC ACIDURIA DISORDER (OAD)

Variable	Estimates	Sources
Annual OAD inborn babies[1]	130	Ozane et al. (2012), Haberle et al. (2018), Chapman et al. (2018), Couce et al. (2011), Dionisi-Vici et al. (2002), Sanderson et al. (2006)
Age range of HAC	0-4 y.o.	Kiykim et al. (2021)
Annual HAC occurrence	105%	Walker et al. (2012)

All data used in this assessment is in 2021, reference publications are only longitudinal/real-world data used, epidemiology projections modelling references are excluded.

NUMBERS OF ANNUAL INBORN WITH UCD AND OA BASED ON PREVALENCE IN US AND EU5



Sources: Maillot et al. (2007), Batshaw et al. (2015), Nettesheim (2017), Martin-Hernandez (2014)

Ultra-orphan disease is defined as conditions occurring with a "prevalence of less than 1 in 50,000" (NICE, 2004)

Conclusion

To author's knowledge, this study provides the first calculation on incidence of HAC in patients with UCD and OAD. Estimated 1'898 HAC (around 1:368'000) in 2021, thus classified as ultra-orphan disease (<1:50'000). This estimate can be used to calculate burden of diseases and economic evaluation for acute HAC in Inborn Errors of Metabolism.

References

1. Batshaw, M. L., Lee, B., Diaz, G. A., Rhead, W., Lichter-Konecki, U., Feigenbaum, A., Berry, S. A., le Mons, C., Bartley, J. A., Longo, N., Nagamani, S. C., Berquist, W., Gallagher, R., Bartholomew, D., Harding, C. O., Korson, M. S., McCandless, S. E., Smith, W., Cederbaum, S., … Yudoff, M. (2015). Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. Genetics in Medicine, 17(7), 561–568. https://doi.org/10.1038/gim.2014.148

2. Nettesheim, S., Kölker, S., Karall, D., Häberle, J., Posset, R., Hoffmann, G. F., Heinrich, B., Gleich, F., & Garbade, S. F. (2017). Incidence, disease onset and short-term outcome in urea cycle disorders -cross-border surveillance in Germany, Austria and Switzerland. Orphanet Journal of Rare Diseases, 12(1). https://doi.org/10.1186/s13023-017-0661-x

3. Martín-Hernández, E., Aldámiz-Echevarría, L., Castejón-Ponce, E., Pedrón-Giner, C., Couce, M. L., Serrano-Nieto, J., Pintos-Morell, G., Bélanger-Quintana, A., Martínez-Pardo, M., García-Silva, T., Quijada-Fraile, P., Vitoria-Miñana, I., Dalmau, J., Lama-More, R. A., Amor Bueno-Delgado, M., del Toro-Riera, M., García-Jiménez, I., Sierra-Córcoles, C., Ruiz-Pons, M., … Pérez-Cerdá, C. (2014). Urea cycle disorders in Spain: an observational, cross-sectional and multicentric study of 104 cases. http://www.ojrd.com/content/9/1/187

4. Acer therapeutics SEC 8-K (2020)

5. Summar, M. L., Koelker, S., Freedenberg, D., le Mons, C., Haberle, J., Lee, H. S., & Kirmse, B. (2013). The incidence of urea cycle disorders. Molecular Genetics and Metabolism, 110(1–2), 179–180. https://doi.org/10.1016/j.ymgme.2013.07.008

6. Ozanne, B., Nelson, J., Cousineau, J., Lambert, M., Phan, V., Mitchell, G., Alvarez, F., Ducruet, T., & Jouvet, P. (n.d.). Threshold for toxicity from hyperammonemia in critically ill children.

7. Häberle, J., Chakrapani, A., Ah Mew, N., & Longo, N. (2018). Hyperammonaemia in classic organic acidaemias: A review of the literature and two case histories. In Orphanet Journal of Rare Diseases (Vol. 13, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13023-018-0963-7

8. Chapman, K. A., Gramer, G., Viall, S., & Summar, M. L. (2018). Incidence of maple syrup urine disease, propionic acidemia, and methylmalonic aciduria from newborn screening data. Molecular Genetics and Metabolism Reports, 15, 106–109. https://doi.org/10.1016/j.ymgmr.2018.03.011

9. Couce, M. L., Castiñeiras, D. E., Bóveda, M. D., Baña, A., Cocho, J. A., Iglesias, A. J., Colón, C., Alonso-Fernández, J. R., & Fraga, J. M. (2011). Evaluation and long-term follow-up of infants with inborn errors of metabolism identified in an expanded screening programme. Molecular Genetics and Metabolism, 104(4), 470–475. https://doi.org/10.1016/j.ymgme.2011.09.021

10. Dionisi-Vici, C., Rizzo, C., Burlina, A. B., Caruso, U., Sabetta, G., Uziel, G., & Abeni, D. (2002). Inborn errors of metabolism in the Italian pediatric population: A national retrospective survey. Journal of Pediatrics, 140(3), 321–329. https://doi.org/10.1067/mpd.2002.122394

11. Sanderson, S., Green, A., Preece, M. A., & Burton, H. (2006). The incidence of inherited metabolic disorders in the West Midlands, UK. Archives of Disease in Childhood, 91(11), 896–899. https://doi.org/10.1136/adc.2005.091637

12. Kiykim, E., Oguz, O., Duman, C., Zubarioglu, T., Cansever, M. S., & Zeybek, A. C. A. (2021). Long-term N-carbamylglutamate treatment of hyperammonemia in patients with classic organic acidemias. Molecular Genetics and Metabolism Reports, 26. https://doi.org/10.1016/j.ymgmr.2021.100715

13. Walker, V. (2012). Severe hyperammonaemia in adults not explained by liver disease. In Annals of Clinical Biochemistry (Vol. 49, Issue 3, pp. 214–228). https://doi.org/10.1258/acb.2011.011206