Genetic background and clinical characteristics of infantile hyperammonaemia

Mengyao Li
Children's Hospital of Fudan University, National Children's Medical Center
Xiang Chen
Children's Hospital of Fudan University, National Children's Medical Center
Huiyao Chen
Children's Hospital of Fudan University, National Children's Medical Center
Liyuan Hu
Children's Hospital of Fudan University, National Children's Medical Center
Yun Cao
Children's Hospital of Fudan University, National Children's Medical Center
Guoqiang Cheng
Children's Hospital of Fudan University, National Children's Medical Center
Laishuan Wang
Children's Hospital of Fudan University, National Children's Medical Center
Bingbing Wu
Children's Hospital of Fudan University, National Children's Medical Center
Wei Lu
Children's Hospital of Fudan University, National Children's Medical Center
Lin Yang (linyang09@fudan.edu.cn)
Children's Hospital of Fudan University, National Children's Medical Center
Wenhao Zhou
Children's Hospital of Fudan University, National Children's Medical Center

Research Article

Keywords: genetics, hyperammonaemia, infants, neonates

Posted Date: April 8th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1527973/v1

Abstract

Purpose: This study was conducted to analyse the genetic spectrum and clinical characteristics of infantile hyperammonaemia (HA).

Methods: Between January 2016 and June 2020, we enrolled patients with definitive genetic diagnosis of infantile HA at the Children's Hospital of Fudan University. Based on the age of HA onset, patients were grouped into neonatal and post-neonatal subgroups to compare their genetic and clinical features.

Results: Collectively, 136 pathogenic or likely pathogenic variants of the 33 genes were identified. Fourteen genes were reported with HA (42%, 14/33), with *SLC25A13* and *MUT* being the top two detected genes. In contrast, 19 genes were not reported with HA (58%, 19/33), in which *JAG1* and *ABCC8* were the most frequently mutated genes. Compared with post-neonatal HA, neonatal HA patients presented with higher rates of organic acidemia ($p = 0.001$) and fatty acid oxidation disorder ($p = 0.006$), but a lower rate of cholestasis ($p < 0.001$). Neonatal HA patients had a higher ratio of peak plasma ammonia level ≥ 500 μmol/L ($p = 0.003$) and were more likely to receive precision medicine ($p = 0.027$); however, they had a refractory clinical course ($p = 0.001$) and poorer prognosis than the infantile group.

Conclusions: There were significant differences in the genetic spectrum, clinical features, clinical course, and outcomes between infants with different HA onset ages.

What Is Known

•Urea cycle defects, organic acidemia, and fatty acid oxidation disorders are the most common inborn errors of metabolism associated with hyperammonaemia.

What is New:

•Genetic spectra, clinical features, clinical course, and outcomes vary with age of infantile hyperammonaemia onset.

•Genetic features underlying cholestasis may be associated with hyperammonaemia.

Introduction

Hyperammonaemia (HA) refers to an increased blood ammonia level, which can cause irreversible damage to the central nervous system, especially in paediatric patients [1]. Normal plasma ammonia levels in premature new-borns, full-term new-borns, infants, and children decrease with time, but their reference values have not been well defined so far [2-4]. In this study, we used plasma ammonia ≥ 100 μmol/L as the diagnostic threshold for infantile hyperammonaemia.

HA is primarily caused by severe liver diseases, infections, and certain drugs. However, in children, especially infants, inborn errors of metabolism (IEM) play an important role in the development of HA [5-

8]. IEM is a heterogeneous group of disorders with complex clinical manifestations. Most patients with inherited HA exhibit non-specific symptoms, such as poor feeding, lethargy, dyspnoea, or hypothermia, which rapidly progress to convulsions or coma; these general symptoms make it difficult to differentiate HA from conditions such as sepsis [9, 10]. The time window for clinical diagnosis is very short, and timely aetiology-based therapy is critical. The diagnostic rate of IEM has improved with the use of mass spectrometry. However, the spectrum of diseases that can be detected by mass spectrometry is limited, and the detection results are affected by several factors such as patient condition and the treatment given, which may cause misdiagnosis and underdiagnosis [11].

Next-generation sequencing (NGS) is applicable to a wide spectrum of diseases, and the outcomes are generally independent of typical clinical manifestations and biochemical characteristics, which are used for the early diagnosis of disease and indicate possible underlying genetic causes [12]. NGS has been applied to the early diagnosis and precision therapy of many disorders, such as infantile epilepsy, neonatal metabolic acidosis, and neonatal hypernatraemia [13-15]. For infantile HA, precision treatment based on orphan drugs, liver stem cell transplantation, gene therapy, and prenatal treatment has been increasingly reported [16-20]. All of these previous studies were based on the application of genetic analysis to diagnosis, and NGS was the key diagnostic method used [21].

The known genetic causes of infantile HA mainly include urea cycle disorder (UCD), organic acidemia (OA), and fatty acid oxidation disorder (FAOD) [6-8, 22, 23]. A wide range of genes have been identified and reported in the human phenotype ontology associated with infantile hyperammonaemia [24-26]. However, in clinical practice, the status of several other genes, such as *ABCC8* [27] and *GALT* [28, 29], in hyperammonaemia remains unknown. In the present study, we conducted a retrospective analysis of a cohort with genetically confirmed diagnosis of infantile HA to expand its genetic background. To the best of our knowledge, this is the most comprehensive study to determine the genetic background of infantile HA.

Materials And Methods

Study population

We enrolled infants diagnosed with HA at the Children's Hospital of Fudan University from January 2016 to June 2020. The inclusion criteria were as follows: (1) HA onset before 1 year of age, (2) plasma ammonia level ≥100 μmol/L as indicated by more than two tests during the same hospital stay, and (3) genetic diagnosis using NGS. The exclusion criteria were as follows: (1) liver failure secondary to severe infection, respiratory failure or graft-versus-host disease, severe gastrointestinal bleeding, long-term total parenteral nutrition, and history of valproate use; and (2) failure to obtain informed consent from the parents. This study was approved by the Ethics Committee of the Children's Hospital of Fudan University (2015-130).

Clinical subgroup classification

Clinical information was obtained from the medical record system. The clinical course of each case was classified as follows: (1) refractory, blood ammonia level ≥ 100 μmol/L after treatment; (2) controllable, blood ammonia level < 100 μmol/L after treatment; and (3) self-limiting, blood ammonia level <100 μmol/L without treatment. Follow-up information was extracted from the outpatient medical record system, and cases with missing follow-up information were followed up by telephone.

NGS

Genomic DNA was extracted from the blood samples of patients using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and enriched using the Agilent (Santa Clara, CA, USA) ClearSeq Inherited Disease panel kit for 2742 gene sequencing or the Agilent SureSelect XT Human All Exon V5 for clinical exome sequencing. NGS was performed using the Illumina HiSeq2000/2500 platform. The identified variants were classified based on the American College of Medical Genetics (ACMG) guidelines [30]. The detected causal variants were confirmed by performing Sanger sequencing on a Biosystems 3500 DNA Analyser and analysed using Mutation Surveyor V4.0.9. More details are available in our previous studies [15, 31].

Statistical analysis

The data were analysed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables with non-normal variables are reported as median (interquartile range (IQR)). Categorical variables are presented as frequencies and percentages. The chi-square test or Fisher's exact test was used for comparison. Significance was set at $p < 0.05$.

Results

Study population

We enrolled 85 infants with definitive molecular diagnosis of HA. The median age of onset was 54 days (IQR 10–114 days). The study included 54 male (64%, 54/85) and 31 female (36%, 31/85) patients who were divided into two subgroups according to age of onset: neonate group (32 cases, 38%) and infant group (53 cases, 62%). The dominant phenotypes (a patient may have had more than one clinical phenotype) were neurological abnormality (31%), glucose metabolism disturbance (26%), metabolic acidosis (24%), respiratory failure (15%), and electrolyte disturbance (14%) (Table 1).

Genetic spectrum of infantile HA

Collectively, 136 pathogenic or likely pathogenic (P/LP) variants were identified in 33 genes, with 110 reported variants and 26 novel variants (Supplementary Table 1). Fourteen genes were reported with HA (42%, 14/33), with *SLC25A13* and *MUT* being the top two detected genes (22%, 18/85). Nineteen genes, which have not been previously reported with HA, were detected in this study (58%, 19/33), of which *JAG1* and *ABCC8* were the most frequently mutated genes (16%, 14/85).

Recurrent genetic disorders included cholestasis (55%, 47/85), OA (14%, 12/85), UCD (7%, 6/85), and FAOD (6%, 5/85), with *SLC25A13*, *MUT*, *CPS1,* and *SLC25A20* being the most frequently detected genes in each classification, respectively.

Genetic features of infantile HA depending on onset age

Subgroups with different age of onset showed different genetic disorders. The proportions of OA (p = 0.001), FAOD (p = 0.006), and cholestasis (p < 0.001) showed significant differences between the two subgroups (Table 1). *MUT* (19 %, 6/32) was the most frequently detected gene in the neonatal group, whereas in the post-neonatal group, the most frequently mutated gene was *SLC25A13* (21%, 11/53).

In cases of refractory HA (21%, 18/85), all mutated genes in the neonatal group were reported with HA, with *MUT* being the most frequently identified gene (Figure 1). In the post-neonatal group, mutated *ABCB11*, *CYP7B1*, and *MPV17*, which have not been previously reported with the HA phenotype, were associated with refractory HA; interestingly, all these cases presented with liver failure.

In controllable or self-limiting HA cases (79%, 67/85), mutations in *SLC25A13*, *JAG1,* and *ABCC8* were detected in more than five cases, accounting for 37% (25/67) of all cases. Mutated *SLC25A13* and most mutated *JAG1* (7/8) were detected in the infantile group, and all cases presented a cholestatic phenotype. In the neonatal group, *ABCC8* was the most frequently mutated gene, and all cases presented with hypoglycaemia. Notably, mutated *JAG1* and *ABCC8* with the hypoglycaemic phenotype have not been previously reported with HA.

Clinical characteristics of inherited HA according to the age of onset

To investigate the characteristics of inherited HA according to the age of onset, we compared the clinical phenotypes of the neonatal and infantile groups. We found significant differences in the clinical features, clinical course, and outcomes between the two subgroups.

In the neonatal subgroup, 25% cases (8/32) presented with a peak plasma ammonia level ≥ 500 μmol/L, compared to 2% cases in the infantile group (1/53, p = 0.003). Neonatal patients with HA showed higher rates of neurological abnormalities (p < 0.001), respiratory failure (p < 0.001), metabolic acidosis (p = 0.001), glucose metabolism disturbance (p = 0.016), and electrolyte disturbances (p = 0.010) than infantile patients (Table 1). Infants with HA were more likely to present with hepatic failure than neonates (p = 0.042).

Among the neonatal subgroup, 41% patients (13/32) presented with a refractory clinical course, compared to just 9% patients in the infant group (5/53, p = 0.001). Clinical outcomes in the infant group were generally better than those in the neonatal group, with 83% patients showing improvement (44/53) and only 13% patients (7/53) withdrawing the treatment in consideration of the poor prognosis. In contrast, in the neonatal group, only 38% (12/32) patients had good prognoses (p < 0.001), and 47% (15/32) patients withdrew from the treatment (p = 0.001) given the poor prognosis.

Discussion

We observed a significantly different genetic spectrum between patients with neonatal and post-neonatal HA. In our cohort, the genetic spectrum of neonatal HA mainly included OA, FAOD, and UCD, while the proportion of these disorders was lower in the post-natal subgroup, which is consistent with the etiological profile reported previously [6-8, 22, 23]. Defects in the function of any enzyme or carrier involved in the urea cycle can cause primary HA. HA caused by OA and FAOD is secondary to the functional inhibition of enzymes involved in the urea cycle by their metabolites and the reduction in substrates required for urea synthesis [5]. We speculate that this difference in the genetic spectrum between subgroups based on the age of onset is because the severity of UCD, OA, and FAOD is related to the degree of enzyme-related defects in the corresponding metabolic pathways [32]. Patients with reduced enzyme activity may have an earlier onset of the disease, exhibit more severe clinical presentations (higher plasma ammonia level), and may not survive the neonatal period. In other words, patients with UCD, OA, or FAOD onset after one month of age may exhibit lower ammonia levels, and therefore, were not included in our cohort. This also explains why patients in the neonatal subgroup showed higher rates of a refractory clinical course and poor prognosis.

In this study, hereditary liver disease was the main genetic cause of HA onset before one year of age. Neonatal-onset type II citrullinemia (MIM 605814, *SLC25A13*) (neonatal intrahepatic cholestasis caused by citrin deficiency, NICCD) is the most common hereditary liver disease. NICCD is known to cause mild, self-limiting HA. NICCD pathogenesis involves citrin deficiency caused by the pathogenic variants of *SLC25A13*, which leads to the insufficient transfer of aspartic acid into the cytoplasm and affects its utilisation for urea cycle substrate synthesis [10]. Other cholestasis-related genes, such as *JAG1*, *ABCC2*, and *ABCB11*, have not been reported to cause HA phenotype. In our study, most patients with cholestasis did not show significantly elevated transaminase levels, suggesting that in patients presenting with HA along with cholestasis, the phenotype may be related to cholestasis itself.

Pathogenic variants of *ABCC8* were frequently observed in our cohort (7%, 6/85). Neonatal diabetes caused by *ABCC8* defects may be associated with HA phenotype [27]. The authors speculated that elevated serum leucine and glutamic acid levels during ketoacidosis promote the oxidative deamination of glutamic acid to increase blood ammonia levels. However, in our study, the six patients with *ABCC8* defects presented with hyperinsulinaemia rather than diabetes. Therefore, *ABCC8*-specific pathogenesis needs to be clarified further. HA can present with hyperinsulinism/hyperammonaemia syndrome (MIM 606762, *GLUD1*), wherein an excessive increase in the activity of *GLUD1*-encoded glutamate dehydrogenase (GDH) increases glutamate oxidative deamination and glutamate consumption, which leads to a reduction in N-acetylglutamate (NAG), the activator of the urea cycle rate-limiting enzyme, thus indirectly affecting urea synthesis [33]. GDH overactivity can increase the ATP/ADP ratio in islet cells, thereby closing the K^+-ATP channel, depolarising the cell membrane, and opening the calcium channel, leading to insulin release. Variants of *ABCC8* cause abnormalities in the K^+-ATP channel in islet cells [34], which may be associated with GDH activity to some extent.

Two patients in our cohort had galactosaemia (MIM 230400, *GALT*). Although one patient had liver failure, the HA was controllable. In a previous case report of galactosemia, a neonatal patient with mildly elevated transaminase levels developed transient HA. The authors speculated that this may be due to the toxic effects of galactose on hepatocytes [28]. In a phenotype-genotype analysis of five patients with galactosemia, one patient with HA carried the C. 687 g >A variant as one of the patients in the cohort of our present study [29]. This suggests a correlation between the *GALT* genotype and HA; however, this needs to be confirmed in the future studies.

We also observed HA in two patients with glycogen storage disease II (MIM 232300, *GAA*) in which transaminase levels are slightly elevated. This may be related to the upregulated purine nucleotide cycle for supplying energy when glycogen storage is impaired; however, this can produce ammonia. A previous study proposed elevated blood ammonia levels as a screening index for metabolic myopathy [35], and our results support that HA may be a metabolic myopathy. We also observed HA in three children with haemolytic anaemia and G6PD deficiency (favism) (MIM 300908, *G6PD*), including one with cholestasis, one with severe infection, and another with bilirubin encephalopathy. Since patients exhibiting severe haemolysis (such as severe fracture and trauma) may present with HA [10], HA in patients with G6PD deficiency may be related to severe haemolysis.

This study expanded the spectrum of pathogenic variants associated with infantile HA and enriched its possible genetic background. However, this study has some limitations. First, NGS cannot detect all pathogenic variants, and so, its use in clinical setting may lead to underdiagnosis. Second, we did not elucidate the mechanism underlying the correlation between the variants detected in this study and HA, so further research is needed to fully understand this relationship. Finally, this was a retrospective single-centre study with few participants and limited phenotypic data, which may result in bias. Therefore, a prospective multi-centre study including more participants should be carried out in the future.

Conclusion

In this study, we performed NGS to expand the genetic background and clinical characteristics of infantile HA. In clinical practice, when IEM is considered, blood ammonia should be routinely tested. We recommend early NGS analysis if HA is suspected. Based on the toxic effects of various metabolic products on hepatocytes and the extensive linkages between various metabolic pathways, the genetic profile and related metabolic pathways of HA deserve further study.

Abbreviations

FAOD Fatty acid oxidation disorder

HA Hyperammonaemia

IEM Inborn errors of metabolism

NGS Next-generation sequencing

OA Organic acidemia

UCD Urea cycle disorder

Statements And Declarations

Acknowledgements:

This study was supported by the Shanghai Municipal Science and Technology Major Project (Grant No. 20Z11900600).

Authors' contributions: Mengyao Li and Xiang Chen contributed equally to this article. All the authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by Li and Chen. Mengyao Li and Xiang Chen wrote the manuscript's first draft. All authors have contributed to manuscript revision and read and approved the final manuscript.

Availability of data and materials: Original data are presented in the article or supplementary material. Additional information can be obtained from the corresponding author upon reasonable request.

Funding: This study was supported by the Shanghai Municipal Science and Technology Major Project (Grant No. 20Z11900600).

Ethics approval: This retrospective study involving human participants was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Research Ethics Committee of the Children's Hospital of Fudan University (CHFudan U _NNICU11).

Consent to participate: Written informed consent was obtained from legal guardians.

Consent to publication: Legal guardians signed informed consent regarding publishing the patients' and their data.

Competing interests: The authors have no commercial or financial relationships that could be construed as potential conflicts of interest.

References

1. Braissant O, VA McLin, C Cudalbu (2013) Ammonia toxicity to the brain. Journal of Inherited Metabolic Disease 36(4):595–612.http://doi.org/10.1007/s10545-012-9546-2
2. Madigan T, DR Block, WA Carey, BD Kaemingk, R Patel (2020) Proposed Plasma Ammonia Reference Intervals in a Reference Group of Hospitalized Term and Preterm Neonates. J Appl Lab Med 5(2):363–369.http://doi.org/10.1093/jalm/jfz001

3. Haberle J (2011) Clinical practice: the management of hyperammonemia. Eur J Pediatr 170(1):21–34.http://doi.org/10.1007/s00431-010-1369-2
4. Cormack BE, Y Jiang, JE Harding, CA Crowther, A Lynn, A Nair, M Hewson, M Meyer, R Broadbent, D Webster et al. (2020) Plasma ammonia concentrations in extremely low birthweight infants in the first week after birth: secondary analysis from the ProVIDe randomized clinical trial. Pediatr Res 88(2):250–256.http://doi.org/10.1038/s41390-019-0730-z
5. Walker V (2014) Ammonia metabolism and hyperammonemic disorders. Adv Clin Chem 67(73–150.http://doi.org/10.1016/bs.acc.2014.09.002
6. Vergano SA, JM Crossette, FC Cusick, BR Desai, MA Deardorff, N Sondheimer (2013) Improving surveillance for hyperammonemia in the newborn. Mol Genet Metab 110(1–2):102–105.http://doi.org/10.1016/j.ymgme.2013.05.005
7. Chow SL, V Gandhi, S Krywawych, PT Clayton, JV Leonard, AA Morris (2004) The significance of a high plasma ammonia value. Arch Dis Child 89(6):585–586.http://doi.org/10.1136/adc.2003.036236
8. Abily-Donval L, L Dupic, C Joffre, A Brassier, JB Arnoux, M Grimaud, F Lesage, L de Saint Blanquat, S Bekri, S Marret et al. (2020) Management of 35 critically ill hyperammonemic neonates: Role of early administration of metabolite scavengers and continuous hemodialysis. Arch Pediatr 27(5):250–256.http://doi.org/10.1016/j.arcped.2020.05.002
9. Häberle J, A Burlina, A Chakrapani, M Dixon, D Karall, M Lindner, H Mandel, D Martinelli, G Pintos-Morell, R Santer et al. (2019) Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis 42(6):1192–1230.http://doi.org/10.1002/jimd.12100
10. Summar ML, NA Mew (2018) Inborn Errors of Metabolism with Hyperammonemia: Urea Cycle Defects and Related Disorders. Pediatr Clin North Am 65(2):231–246.http://doi.org/10.1016/j.pcl.2017.11.004
11. Ozben T (2013) Expanded newborn screening and confirmatory follow-up testing for inborn errors of metabolism detected by tandem mass spectrometry. Clin Chem Lab Med 51(1):157–176.http://doi.org/10.1515/cclm-2012-0472
12. Park KJ, S Park, E Lee, JH Park, JH Park, HD Park, SY Lee, JW Kim (2016) A Population-Based Genomic Study of Inherited Metabolic Diseases Detected Through Newborn Screening. Ann Lab Med 36(6):561–572.http://doi.org/10.3343/alm.2016.36.6.561
13. Hu L, L Yang, K Yan, B Wu, H Wang, R Zhang, J Wang, Y Cao, G Cheng, W Zhou (2021) Importance of Early Genetic Sequencing in Neonates Admitted to NICU with Recurrent Hypernatremia: Results of a Prospective Cohort Study. Neonatology 1–8.http://doi.org/10.1159/000519634
14. Ma H, Z Tang, F Xiao, L Li, Y Li, W Tang, L Chen, W Kang, Y Lu, X Dong et al. (2021) Neonatal Metabolic Acidosis in the Neonatal Intensive Care Unit: What Are the Genetic Causes? Front Pediatr 9(727301.http://doi.org/10.3389/fped.2021.727301
15. Yang L, Y Kong, X Dong, L Hu, Y Lin, X Chen, Q Ni, Y Lu, B Wu, H Wang et al. (2019) Clinical and genetic spectrum of a large cohort of children with epilepsy in China. Genet Med 21(3):564–

571.http://doi.org/10.1038/s41436-018-0091-8

16. Sugiyama Y, M Shimura, M Ogawa-Tominaga, T Ebihara, Y Kinouchi, K Isozaki, T Matsuhashi, M Tajika, T Fushimi, K Ichimoto et al. (2020) Therapeutic effect of N-carbamylglutamate in CPS1 deficiency. Mol Genet Metab Rep 24(100622.http://doi.org/10.1016/j.ymgmr.2020.100622
17. Chakrapani A, V Valayannopoulos, NG Segarra, M Del Toro, MA Donati, A García-Cazorla, MJ González, C Plisson, V Giordano (2018) Effect of carglumic acid with or without ammonia scavengers on hyperammonaemia in acute decompensation episodes of organic acidurias. Orphanet J Rare Dis 13(1):97.http://doi.org/10.1186/s13023-018-0840-4
18. Spada M, F Porta, D Righi, C Gazzera, F Tandoi, I Ferrero, F Fagioli, MBH Sanchez, PL Calvo, E Biamino et al. (2020) Intrahepatic Administration of Human Liver Stem Cells in Infants with Inherited Neonatal-Onset Hyperammonemia: A Phase I Study. Stem Cell Rev Rep 16(1):186–197.http://doi.org/10.1007/s12015-019-09925-z
19. Wang L, Y Yang, C Breton, P Bell, M Li, J Zhang, Y Che, A Saveliev, Z He, J White et al. (2020) A mutation-independent CRISPR-Cas9-mediated gene targeting approach to treat a murine model of ornithine transcarbamylase deficiency. Sci Adv 6(7):eaax5701.http://doi.org/10.1126/sciadv.aax5701
20. Wilnai Y, YJ Blumenfeld, K Cusmano, SR Hintz, D Alcorn, WE Benitz, WE Berquist, JA Bernstein, RO Castillo, W Concepcion et al. (2018) Prenatal treatment of ornithine transcarbamylase deficiency. Mol Genet Metab 123(3):297–300.http://doi.org/10.1016/j.ymgme.2018.01.004
21. Wang HJ, WH Zhou (2018) [Intervention of neonatal genetic diseases in the era of precision medicine: challenges and opportunities]. Zhonghua Er Ke Za Zhi 56(4):244–246.http://doi.org/10.3760/cma.j.issn.0578-1310.2018.04.002
22. Arbeiter AK, B Kranz, AM Wingen, KE Bonzel, C Dohna-Schwake, L Hanssler, U Neudorf, PF Hoyer, R Büscher (2010) Continuous venovenous haemodialysis (CVVHD) and continuous peritoneal dialysis (CPD) in the acute management of 21 children with inborn errors of metabolism. Nephrol Dial Transplant 25(4):1257–1265.http://doi.org/10.1093/ndt/gfp595
23. Deodato F, S Boenzi, C Rizzo, D Abeni (2004) Inborn errors of metabolism: an update on epidemiology and on neonatal-onset hyperammonemia. Acta Pñdiatr Suppl 445: 18 ± 21. 2004 10.0180/08035320310021183
24. Jiang HH, Y Guo, X Shen, Y Wang, TT Dai, H Rong, R Cheng, F Zhao (2021) Neonatal maple syrup urine disease in China: two novel mutations in the BCKDHB gene and literature review. J Pediatr Endocrinol Metab 34(9):1147–1156.http://doi.org/10.1515/jpem-2020-0746
25. Ali A, FSA Almesmari, NA Dhahouri, AM Saleh Ali, M Aldhanhani, R Vijayan, A Al Tenaiji, A Al Shamsi, J Hertecant, F Al Jasmi (2021) Clinical, Biochemical, and Genetic Heterogeneity in Glutaric Aciduria Type II Patients. Genes (Basel) 12(9):10.3390/genes12091334
26. Kohler S, M Gargano, N Matentzoglu, LC Carmody, D Lewis-Smith, NA Vasilevsky, D Danis, G Balagura, G Baynam, AM Brower et al. (2021) The Human Phenotype Ontology in 2021. Nucleic Acids Res 49(D1):D1207-D1217.http://doi.org/10.1093/nar/gkaa1043

27. Thakkar AN, MN Muranjan, S Karande, NS Shah (2014) Neonatal diabetes mellitus due to a novel ABCC8 gene mutation mimicking an organic acidemia. Indian J Pediatr 81(7):702–704.http://doi.org/10.1007/s12098-013-1102-z
28. Cheung KL, NL Tang, KJ Hsiao, LK Law, W Wong, PC Ng, CP Pang, DA Applegarth, TF Fok, NM Hjelm (1999) Classical galactosaemia in Chinese: A case report and review of disease incidence. J Paediatr Child Health 35(4):399–400.http://doi.org/
29. Yang RL, F Tong, F Hong, GL Qian, DW Wu, ZY Zhao (2017) [Analysis of newborn screening for galactosemia and genotype-phenotype of confirmed galatosemia cases]. Zhonghua Er Ke Za Zhi 55(2):104–109.http://doi.org/10.3760/cma.j.issn.0578-1310.2017.02.010
30. Richards S, N Aziz, S Bale, D Bick, S Das, J Gastier-Foster, WW Grody, M Hegde, E Lyon, E Spector et al. (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17(5):405–424.http://doi.org/10.1038/gim.2015.30
31. Yang L, X Dong, X Peng, X Chen, B Wu, H Wang, Y Lu, W Zhou (2018) Evaluation of turn around time and diagnostic accuracy of the next generation sequencing data analysis pipeline version 2 of Children's Hospital of Fudan University. Chinese Journal of Evidence Based Pediatrics 13(2):118–123.http://doi.org/
32. Wakiya T, Y Sanada, T Urahashi, Y Ihara, N Yamada, N Okada, K Ushijima, S Otomo, K Sakamoto, K Murayama et al. (2012) Impact of enzyme activity assay on indication in liver transplantation for ornithine transcarbamylase deficiency. Mol Genet Metab 105(3):404–407.http://doi.org/10.1016/j.ymgme.2011.12.019
33. Stanley CA (2004) Hyperinsulinism/hyperammonemia syndrome: insights into the regulatory role of glutamate dehydrogenase in ammonia metabolism. Mol Genet Metab 81 Suppl 1(S45–51.http://doi.org/10.1016/j.ymgme.2003.10.013
34. Arya VB, Q Aziz, A Nessa, A Tinker, K Hussain (2014) Congenital hyperinsulinism: clinical and molecular characterisation of compound heterozygous ABCC8 mutation responsive to Diazoxide therapy. Int J Pediatr Endocrinol 2014(1):24.http://doi.org/10.1186/1687-9856-2014-24
35. Hogrel JY, JBE Janssen, I Ledoux, G Ollivier, A Behin, T Stojkovic, B Eymard, NC Voermans, P Laforet (2017) The diagnostic value of hyperammonaemia induced by the non-ischaemic forearm exercise test. J Clin Pathol 70(10):896–898.http://doi.org/10.1136/jclinpath-2017-204324

Table

Table 1 Comparison of genetic spectrum and clinical features of infantile hyperammonaemia with different ages of onset (n (%))

Clinical features	Total N=85	Neonatal N=32	<1 year N=53	*p* value
Genetic spectrum				
OA	12 (14)	10 (31)	2 (4)	0.001
FAOD	5 (6)	5 (16)	0 (0)	0.006
UCD	6 (7)	4 (13)	2 (4)	0.416
Cholestasis	47 (55)	6 (19)	41 (77)	< 0.001
Clinical features				
Peak $NH_3 \geq$ 500μmol/L	9 (11)	8 (25)	1 (2)	0.003
neurologic abnormality	26 (31)	21 (66)	5 (9)	0.001
respiratory failure	13 (15)	11 (34)	2 (4)	0.001
circulatory failure	6 (7)	4 (13)	2 (4)	0.192
hepatic failure	7 (8)	0 (0)	7 (13)	0.042
severe infection	8 (9)	5 (16)	3 (6)	0.146
malformation	9 (11)	4 (13)	5 (9)	0.935
metabolic acidosis	20 (24)	14 (44)	6 (11)	0.001
Hyperlactacidemia	6 (7)	3 (9)	3 (6)	0.668
Glucose metabolic disturbance	22 (26)	13 (41)	9 (17)	0.016
electrolyte disturbance	12 (14)	9 (28)	3 (6)	0.010
Treatment				
Arginine	31 (36)	16 (50)	15 (28)	0.051
CRRT	2 (2)	2 (6)	0 (0)	0.133
Precision medicine	30 (35)	16 (50)	14 (26)	0.027
Clinical course of HA				
Self-limited	23 (27)	5 (16)	18 (34)	0.065
Controllable	44 (52)	14 (44)	30 (57)	0.251
Refractory	18 (21)	13 (41)	5 (9)	0.001
Clinical outcomes				
Improved	56 (66)	12 (38)	44 (83)	< 0.001

Withdrew treatment	22 (26)	15 (47)	7 (13)	0.001
Died	7 (8)	5 (16)	2 (4)	0.098

CRRT, continuous renal replacement therapy

Figures

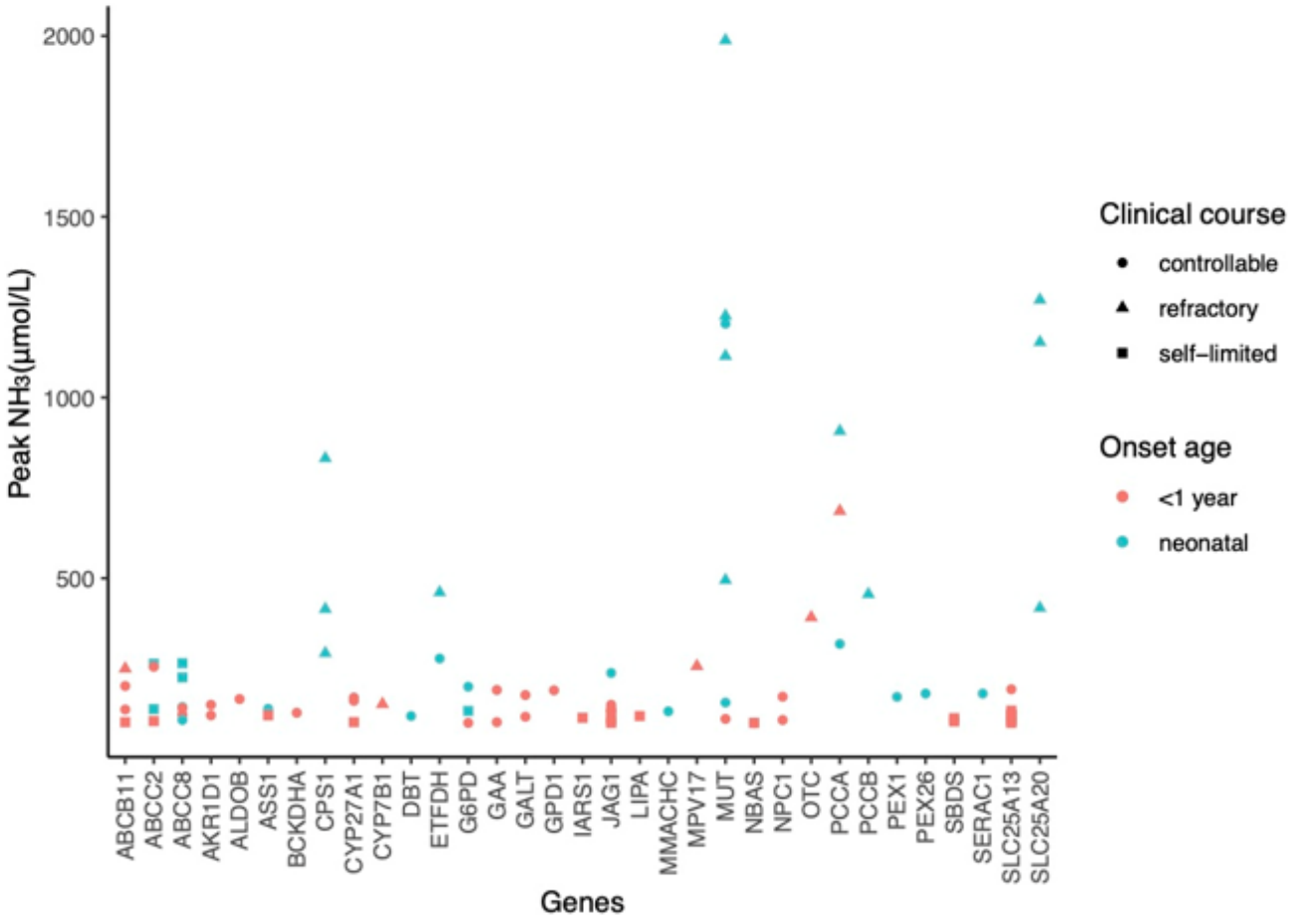

Figure 1

Genetic background and distribution of peak plasma ammonia level in subgroups with different onset age; neonatal hyperammonaemia (denoted by blue) and patients with hyperammonaemia onset before one year old (denoted by yellow). Circles, triangles, and squares represent controllable, refractory, and self-limiting clinical courses respectively (R software 4.0.1 was used to create the artwork)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.xlsx