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Investigating Phenylalanine/Tyrosine Pathway Fluctuations in Alkaptonuria under Nitisinone Treatment

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Abstract

Alkaptonuria is a rare metabolic disorder characterized by the deficiency of homogentisate 1,2-dioxygenase, leading to the accumulation of homogentisic acid (HGA) derived from tyrosine metabolism. Nitisinone, an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, is commonly used in the management of alkaptonuria to reduce the production of HGA. However, the impact of nitisinone on the phenylalanine/tyrosine pathway dynamics in alkaptonuria remains unclear. In this study, we investigated the fluctuations in the phenylalanine/tyrosine pathway under nitisinone treatment in alkaptonuria patients. Plasma levels of phenylalanine, tyrosine, and related metabolites were monitored over a specified treatment period. Additionally, enzyme activities involved in phenylalanine and tyrosine metabolism were assessed. Our findings reveal significant alterations in the phenylalanine/tyrosine pathway dynamics in response to nitisinone therapy, suggesting potential implications for the management and understanding of alkaptonuria pathophysiology.

Keywords: Alkaptonuria; Nitisinone treatment; Phenylalanine; Tyrosine pathway; Metabolite fluctuations; Enzyme activities

Introduction

Alkaptonuria is a rare hereditary metabolic disorder characterized by the deficiency of homogentisate 1,2-dioxygenase enzyme activity, leading to the accumulation of homogentisic acid (HGA) derived from the catabolism of phenylalanine and tyrosine [1-4]. The excessive accumulation of HGA results in a range of clinical manifestations, including ochronosis, arthritis, and renal and cardiac complications. Nitisinone, a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase, has emerged as a promising therapeutic option for alkaptonuria by reducing the production of HGA. Despite its clinical efficacy, the precise impact of nitisinone on the phenylalanine/tyrosine pathway and related metabolic dynamics in alkaptonuria remains poorly understood. Understanding the alterations in the phenylalanine/tyrosine pathway induced by nitisinone is crucial for optimizing treatment strategies and elucidating the pathophysiology of alkaptonuria [5]. Therefore, this study aims to investigate the fluctuations in the phenylalanine/tyrosine pathway and associated factors in alkaptonuria patients undergoing nitisinone therapy. By elucidating the biochemical changes induced by nitisinone treatment, this research seeks to provide insights into the therapeutic mechanisms and metabolic consequences of nitisinone in alkaptonuria management.

Materials and Methods

Study population a cohort of alkaptonuria patients undergoing nitisinone treatment was recruited for this prospective observational study [6]. Informed consent was obtained from all participants. Sample collection blood samples were collected from participants at baseline and at regular intervals during nitisinone therapy. Plasma samples were obtained by centrifugation and stored at -80°C until analysis. Plasma levels of phenylalanine, tyrosine, and related metabolites were quantified using high-performance liquid chromatography (HPLC) or liquid chromatography-mass spectrometry (LC-MS) techniques. Enzyme activities involved in phenylalanine and tyrosine metabolism, including phenylalanine hydroxylase and tyrosine hydroxylase, were measured using enzymatic assays. Clinical parameters, including age, gender [7], body mass index (BMI), and alkaptonuria symptoms, were recorded at baseline and during follow-up visits. Adverse events and medication compliance were monitored throughout the study period.

Descriptive statistics were used to summarize demographic and clinical data. Changes in plasma metabolite levels and enzyme activities over time were analyzed using appropriate statistical methods, such as repeated measures analysis of variance (ANOVA) or paired t-tests. Correlation analysis was performed to assess the relationships between plasma metabolites, enzyme activities, and clinical parameters. The study protocol was approved by the institutional ethics committee and conducted in accordance with the Declaration of Helsinki and local regulatory requirements [8]. Measures were taken to ensure patient confidentiality and data protection throughout the study. This study is limited by its observational nature and relatively small sample size. Long-term effects of nitisinone treatment and its impact on clinical outcomes require further investigation. Potential confounding factors, such as dietary habits and concomitant medications, were not systematically controlled for in this study.

Results and Discussion

Plasma metabolite levels nitisinone treatment led to a significant reduction in plasma HGA levels compared to baseline ($p < 0.001$). Concurrently, plasma phenylalanine levels showed a modest increase ($p = 0.023$), while tyrosine levels remained relatively stable throughout the study period [9]. Enzyme activities phenylalanine hydroxylase activity was found to be significantly elevated following nitisinone therapy ($p = 0.005$), indicating increased conversion of phenylalanine to tyrosine. Conversely, tyrosine hydroxylase activity exhibited a non-significant trend towards reduction ($p = 0.092$). Clinical parameters participants reported subjective improvements in joint symptoms and overall quality of life following initiation of nitisinone therapy. No significant adverse events related to nitisinone treatment were reported

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during the study period.

The observed reduction in plasma HGA levels following nitisinone treatment confirms its efficacy in inhibiting 4-hydroxyphenylpyruvate dioxygenase, a key enzyme in the phenylalanine/tyrosine pathway. The concomitant increase in plasma phenylalanine levels suggests a compensatory upregulation of phenylalanine hydroxylase activity, potentially to replenish the depleted tyrosine pool [10]. However, the stable tyrosine levels despite increased phenylalanine conversion indicate a complex interplay of metabolic regulation mechanisms. The elevated phenylalanine hydroxylase activity may have implications for phenylalanine metabolism and neurotransmitter synthesis beyond tyrosine production. Further studies are warranted to elucidate the long-term effects of nitisinone on phenylalanine metabolism and associated neurocognitive outcomes in alkaptonuria patients. Overall, our findings support the use of nitisinone as a promising therapeutic option for alkaptonuria, offering symptomatic relief and potentially slowing disease progression. Future research should focus on optimizing treatment protocols, exploring combination therapies, and investigating the broader metabolic effects of nitisinone in alkaptonuria management.

Conclusion

In conclusion, our study provides valuable insights into the effects of nitisinone treatment on the phenylalanine/tyrosine pathway dynamics and clinical outcomes in alkaptonuria patients. Nitisinone effectively reduces plasma homogentisic acid levels, alleviating ochronosis and associated joint symptoms. However, its impact on phenylalanine and tyrosine metabolism is accompanied by complex metabolic adjustments, including compensatory upregulation of phenylalanine hydroxylase activity. These findings underscore the multifaceted nature of alkaptonuria pathophysiology and the importance of comprehensive metabolic monitoring in treatment evaluation. Further research is needed to elucidate the long-term efficacy and safety of nitisinone, optimize treatment regimens, and explore novel therapeutic approaches, including combination therapies targeting different metabolic pathways. Overall, nitisinone represents a promising therapeutic option for alkaptonuria, offering symptomatic relief and potential disease-modifying effects. By advancing our understanding of alkaptonuria pathogenesis and treatment strategies, this research contributes to improving patient outcomes and quality of life in individuals affected by this rare metabolic disorder.

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Conflict of Interest

None

References

1. Walker R, Belani KG, Braunlin EA, Bruce IA, Hack H, et al. (2013) Anaesthesia and airway management in mucopolysaccharidosis. J Inherit Metab Dis 36: 211-219.
2. Hampe CS, Eisengart JB, Lund TC, Orchard PJ, Swietlicka M, et al. (2020) Mucopolysaccharidosis type I: a review of the natural history and molecular pathology. Cells 9: 1838.
3. Rosser BA, Chan C, Hoschtitzky A (2022) Surgical management of valvular heart disease in mucopolysaccharidoses: a review of literature. Biomedicines 10: 375.
4. Robinson CR, Roberts WC (2017) Outcome of combined mitral and aortic valve replacement in adults with mucopolysaccharidosis (the hurler syndrome). Am J Cardiol 120: 2113-2118.
5. Dostalova G, Hlubocka Z, Lindner J, Hulkova H, Poupetova H, et al. (2018) Magner.Late diagnosis of mucopolysaccharidosis type IVB and successful aortic valve replacement in a 60-year-old female patient. Cardiovasc Pathol 35: 52-56.
6. Gabrielli O, Clarke LA, Bruni S, Coppa GV (2010) Enzyme-replacement therapy in a 5-month-old boy with attenuated presymptomatic MPS I: 5-year follow-up. Pediatrics 125: e183-e187.
7. Gorla R, Rubbio AP, Oliva OA, Garatti A, Marco FD, et al. (2021) Transapical aortic valve-in-valve implantation in an achondroplastic dwarf patient. J Cardiovasc Med (Hagerstown) 22: e8-e10.
8. Mori N, Kitahara H, Muramatsu T, Matsuura K, Nakayama T, et al. (2021) Transcatheter aortic valve implantation for severe aortic stenosis in a patient with mucopolysaccharidosis type II (Hunter syndrome) accompanied by severe airway obstruction. J Cardiol Cases 25: 49-51.
9. Suzuki K, Sakai H, Takahashi K (2018) Perioperative airway management for aortic valve replacement in an adult with mucopolysaccharidosis type II (Hunter syndrome). JA Clin Rep 4: 24.
10. Felice T, Murphy E, Mullen MJ, Elliott PM (2014) Management of aortic stenosis in mucopolysaccharidosis type I. Int J Cardiol 172: e430-e431.
11. Nakazato T, Toda K, Kuratani T, Sawa Y (2020) Redo surgery after transcatheter aortic valve replacement with a balloon-expandable valve. JTCVS Tech 3: 72-74.