CASE REPORT OLGU SUNUMU

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Management of the Patient with Phenylketonuria with Extraarticular Hip Fracture

Ekstraartiküler Kalça Kırığı Olan Fenilketonürili Hastanın Yönetimi

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ABSTRACT Phenylketonuria (PKU) is a genetic metabolic disorder characterized by elevated phenylalanine levels due to a deficiency of the enzyme phenylalanine-4-hydroxylase. This case report describes the management of a 25-year-old male PKU patient who developed a right intertrochanteric hip fracture following a fall during an epileptic seizure. Due to comorbid conditions such as epilepsy and mental retardation, general anesthesia was administered using a combination of midazolam, propofol, and sevoflurane. Preoperative assessments indicated a low cardiac risk, and the surgery was completed without complications. The patient showed good postoperative recovery and was discharged after 72 hours. In this case, we emphasize the importance of individualized anesthesia planning for PKU patients and suggest that the combination of midazolam, propofol, and sevoflurane may be a safe anesthetic approach.

Keywords: Hip fractures; phenylketonurias; anesthetics

ÖZET Fenilketonüri (FKÜ), fenilalanin-4-hidroksilaz enzim eksikliği nedeniyle fenilalanin seviyelerinin yükseldiği genetik bir metabolik bozukluktur. Bu olgu sunumu, epileptik nöbet sırasında düşme sonucu sağ intertrokanterik kalça kırığı gelişen 25 yaşındaki erkek bir FKÜ hastasının yönetimini anlatmaktadır. Epilepsi ve mental retardasyon gibi eşlik eden hastalıklar nedeniyle genel anestezi midazolam, propofol ve sevofluran kombinasyonu kullanılarak uygulanmıştır. Preoperatif değerlendirmeler düşük kardiyak risk göstermiş ve cerrahi sorunsuz bir şekilde tamamlanmıştır. Hasta postoperatif dönemde iyi bir şekilde iyileşmiş ve 72 saat sonra taburcu edilmiştir. Bu olguda, FKÜ'lü hastalarda bireyselleştirilmiş anestezi planlamasının önemini vurgulamayı ve midazolam, propofol ve sevofluran kombinasyonunun güvenli bir anestezi yaklaşımı olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Kalça kırıkları; fenilketonüriler; anestezikler

Phenylketonuria (PKU) is a hereditary metabolic disorder caused by a deficiency in the enzyme L-phenylalanine-4-hydroxylase (PAH). Elevated levels of phenylalanine are observed in body fluids, and treatment primarily involves a low-protein diet that restricts phenylalanine intake.[1,2] Even if patients maintain normal phenylalanine levels, the risk of fractures remains higher than in the general population due to low bone mineral density.[3] Although a controlled diet can prevent central nervous system damage, adverse effects on the kidneys, skeletal structure, and cardiovascular system have been reported.[4] Conditions such as mental retardation and epilepsy associated with the disorder increase the risk of falls and fractures, classifying these patients as high-risk, according to the American Society of Anesthesiologists. In this case report, we aim to share our experience in treating a PKU patient who sustained a hip fracture due to a fall during an epileptic seizure at a secondary-level state hospital.

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CASE REPORT

Written informed consent was obtained from the patient's first-degree relative for the publication of this report. A 25-year-old male with PKU was brought to the emergency department of our hospital by the 112 emergency medical service due to hip pain after falling during an epileptic seizure with a suspected fracture. Physical examination and radiological imaging revealed a limited and painful range of motion in the right hip joint, tenderness upon palpation of the right hip, external rotation, and shortening of the right lower extremity. Additional findings included spasticity in the flexors of the upper extremities, specifically in the elbows and wrists. Radiological imaging, including X-ray and 3D computed tomography, confirmed the presence of a right intertrochanteric fracture, leading to the patient being admitted to the orthopedics and traumatology department for surgical planning.

The patient's medical history included PKU, epilepsy, celiac disease, mental retardation, and an allergy to amoxicillin. His current medications included sodıum valproate 20% oral solution, Levetiracetam 100 mg/mL oral solution, and Supplemental amino acids. Preoperative cardiology and neurology consultations were performed. Preoperative echocardiography showed an ejection fraction of 60% and a systolic pulmonary artery pressure of 16 mmHg, with normal wall motion. The cardiology consultation concluded that the patient could safely undergo surgery with low cardiac risk. The neurology consultation recommended continuing Depakine 400 mg orally twice daily. Preoperative laboratory tests were within normal limits, including complete blood count, liver and kidney function tests, and coagulation parameters. Considering the risk of seizure activity and the potential difficulties in cooperation due to mental retardation, general anesthesia was planned instead of regional anesthesia. Anticonvulsant medications were continued up to the day of surgery.

For premedication, intravenous (IV) midazolam at 0.02-0.03 mg/kg was administered over 2 minutes for its anticonvulsant and anxiolytic effects. End-tidal carbon dioxide monitors were used to monitor the patient's respiratory gases. Blood glucose monitoring was performed using a glucometer, and body temperature was measured with a bedside monitor temperature probe. The patient was monitored within normoglycemic, normocarbic, and normothermic ranges throughout the surgical period. Anesthesia induction was achieved using propofol, administered in increments of 20-40 mg every 10 seconds until clinical signs of anesthesia were observed. For perioperative analgesia, fentanyl was administered intravenously at a dose of 0.5 mg/kg, along with paracetamol at a dose of 10 mg/kg. The patient was administered 0.6 mg/kg of rocuronium bromide IV as a muscle relaxant. The patient was intubated with a video laryngoscope (Figure 1). During the surgical procedure, anesthesia was maintained with sevoflurane, avoiding hyperventilation, with a minimal alveolar concentration kept below 1.5. The operation was completed in 30 minutes without intraoperative complications, and postoperative oral anticonvulsant therapy was resumed once the patient could tolerate oral intake. The patient was closely monitored in the orthopedics department for 72 hours and discharged with postoperative recommendations.

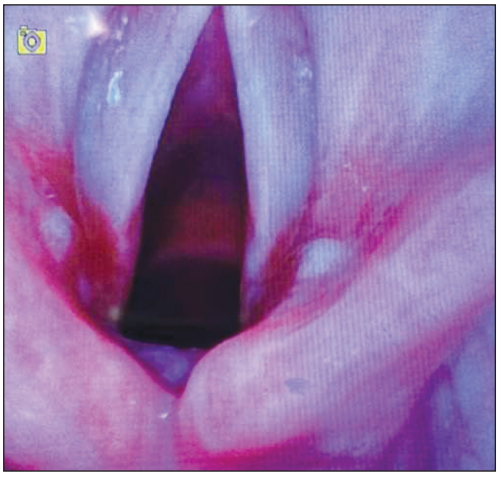

FIGURE 1: Pre-intubation video laryngoscopy image of the patient.

DISCUSSION

PKU is an autosomal recessive inherited disorder resulting from a deficiency in the PAH enzyme, leading to the accumulation of phenylalanine in the body. Symptoms appear when plasma phenylalanine

levels exceed 1,200 µmol/L (>20 mg/dL).[5] The brain is the most affected organ in PKU, with symptoms including seizures, psychiatric problems, skin disorders (eczema, seborrheic dermatitis), microcephaly, hyperreflexia, hypertonia, autism, and mental retardation.[6] The cornerstone of PKU treatment is a low-phenylalanine diet.[7] Our literature review did not identify any specific anesthesia recommendations for PKU patients, prompting us to share our approach in this case.

Greeves et al. reported an increased fracture risk in PKU patients after the age of eight compared to controls, potentially due to poor dietary compliance or elevated plasma phenylalanine concentrations.[8] Our patient was found to have a history of non-compliance with dietary recommendations due to socioeconomic factors, and dietary counseling was provided for future management.

Midazolam, a short-acting benzodiazepine used for premedication, sedation, and anesthesia, acts specifically on GABA-A receptors. Its effects are typically rapid, peaking within 2-3 minutes. Midazolam raises the seizure threshold and has neuroprotective properties, such as preventing lipid peroxidation and mitochondrial damage.[9] Due to the patient's frequent seizures, midazolam was chosen for premedication. Rayadurg et al. reported tachycardia, fever, and severe tachypnea (signs of propofol infusion syndrome) in a 1-year-old PKU patient undergoing sedation with IV bolus (10 mg) and infusion (12 mg) of propofol for magnetic resonance imaging.[10] To avoid similar complications, we administered propofol in 20-40 mg increments every 10 seconds during induction.

Matsushita et al. performed dental surgery under general anesthesia in a PKU patient with mental retardation and epilepsy, using propofol, fentanyl, and rocuronium for induction and propofol-remifentanil infusion and nitrous oxide for maintenance.[11] Opioids may be preferred to provide analgesia and reduce the need for other anesthetic agents. However, it should be noted that accumulated opioid metabolites at high doses may have proconvulsant effects.[12] Lee et al. described a 14-year-old PKU patient with spastic paraparesis who underwent myringoplasty under general anesthesia with nitrous oxide.[13] Considering the central nervous system stimulating effects and low epileptogenic potential of nitrous oxide, we opted for sevoflurane and oxygen for anesthesia maintenance, completing the operation without complications.

Anesthesia management in adult patients with PKU requires careful planning. The choice of anesthesia technique and medications should be made considering comorbid conditions. In this case, a combination of midazolam, rocuronium bromide, fentanyl propofol, and sevoflurane was shown to be a safe option for general anesthesia. However, further case reports and recommendations are needed to establish the optimal anesthesia management for this patient population.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet Can Gezer, Aysun Gezer;* ***Design:*** *Mehmet Can Gezer, Muhammet Sait Bilgiç;* ***Control/Supervision:*** *Aysun Gezer, Deniz Güzel;* ***Data Collection and/or Processing:*** *Deniz Güzel;* ***Analysis and/or Interpretation:*** *Aysun Gezer, Mehmet Can Gezer;* ***Literature Review:*** *Deniz Güzel;* ***Writing the Article:*** *Mehmet Can Gezer, Aysun Gezer;* ***Critical Review:*** *Aysun Gezer;* ***References and Fundings:*** *Deniz Güzel;* ***Materials:*** *Deniz Güzel.*

REFERENCES

1. van Spronsen FJ, van Wegberg AM, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol. 2017;5(9):743-56. [Crossref] [PubMed]
2. van Spronsen FJ, Blau N, Harding C, Burlina A, Longo N, Bosch AM. Phenylketonuria. Nat Rev Dis Primers. 2021;7(1):36. [Crossref] [PubMed] [PMC]
3. Demirdas S, Coakley KE, Bisschop PH, Hollak CE, Bosch AM, Singh RH. Bone health in phenylketonuria: a systematic review and meta-analysis. Orphanet J Rare Dis. 2015;10:17. [Crossref] [PubMed] [PMC]
4. Hansen KE, Binkley N, Ney DM. High fracture rates in young patients with phenylketonuria. Ann Nutr Metab. 2018;72(1):1-2. [Crossref] [PubMed]
5. Shyam R, Sekhar Panda H, Mishra J, Jyoti Panda J, Kour A. Emerging biosensors in phenylketonuria. Clin Chim Acta. 2024;559:119725. [Crossref] [PubMed]
6. Fernstrom JD, Fernstrom MH. Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. J Nutr. 2007;137(6 Suppl 1):1539S-1547S; discussion 1548S. [Crossref] [PubMed]
7. Wiedemann A, Oussalah A, Jeannesson É, Guéant JL, Feillet F. La phénylcétonurie - De la diététique à la thérapie génique [Phenylketonuria, from diet to gene therapy]. Med Sci (Paris). 2020;36(8-9):725-34. French. [Crossref] [PubMed]
8. Greeves LG, Carson DJ, Magee A, Patterson CC. Fractures and phenylketonuria. Acta Paediatr. 1997;86(3):242-4. [Crossref] [PubMed]
9. Olkkola KT, Ahonen J. Midazolam and other benzodiazepines. Handb Exp Pharmacol. 2008;(182):335-60. [Crossref] [PubMed]
10. Rayadurg V, Uttarwar A, Surve R. Is propofol safe in patients with phenylketonuria? J Neurosurg Anesthesiol. 2018;30(1):85-6. [Crossref] [PubMed]
11. Matsushita Y, Momota Y, Kishimoto N, Kotani J. Correspondence. J Dent Sci. 2013;1(8):96-7. [Crossref]
12. Wass CT, Grady RE, Fessler AJ, Cascino GD, Lozada L, Bechtle PS, et al. The effects of remifentanil on epileptiform discharges during intraoperative electrocorticography in patients undergoing epilepsy surgery. Epilepsia. 2001;42(10):1340-4. [Crossref] [PubMed]
13. Lee P, Smith I, Piesowicz A, Brenton D. Spastic paraparesis after anaesthesia. Lancet. 1999;353(9152):554. [Crossref] [PubMed]