



## Is phenylketonuria causes bronchospasm during general anesthesia?

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### ABSTRACT

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Phephenylketonuria (PKU) is caused by an accumulation of phenylalanine in blood and tissue due to phenylalanine hydroxylase enzyme deficiency, which means that phenylalanine, an essential amino acid, cannot be converted to tyrosine. The accumulation of phenylalanine in nonbrain tissues and the decreased production of tyrosine can cause various clinical symptoms. Catecholamines are synthesized via a series of reactions initiated by tyrosine 3,4-dihydroxyphenylalanine hydroxylation. And in the absence of tyrosine, the synthesis of epinephrine can be reduced. There appear to be no studies in the present literature on non-neurological symptoms associated with decreased catecholamine synthesis in patients with PKU. In the present case, we described a severe bronchospasm in a child with PKU during general anesthesia. Further research is needed to confirm whether the bronchospasm that occurred in this case was due to a lack of catecholamine induced by PKU. A link between a deficiency of catecholamines, which are required for neuronal and hormonal control, and pulmonary findings in PKU can be established with clinical and experimental studies.

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### 1. Introduction

Phenylketonuria (PKU) is an autosomal recessive inherited metabolic disease. The prevalence of PKU is 1:10.000-30.000 worldwide and 1:2600 in Turkey (Williams et al., 2008). This high incidence of PKU in Turkey has been linked to the common practice of consanguineous marriages. The disease is caused by an accumulation of phenylalanine in blood and tissue due to phenylalanine hydroxylase enzyme deficiency, which means that phenylalanine, an essential amino acid, cannot be converted to tyrosine (Al Hafid and Christodoulou, 2015). Dysfunction of tetrahydrobiopterin, the cofactor of phenylalanine hydroxylase, may also play a role in PKU. The accumulation of phenylalanine and a lack of tyrosine form the clinical basis of the disease. Although

babies with PKU appear healthy at birth, symptoms begin to develop once they start feeding (Ney et al., 2014). The disease may not be recognized until after the occurrence of irreversible severe mental and motor retardation. A phenylalanine-restricted diet is the most important treatment to prevent further brain damage (Vockley et al., 2014).

Many different clinical findings have been described in patients with PKU, with microcephaly, hypertonia, hyper-reflexia, autism, seizures, and seborrheic and eczematous skin rashes the most common clinical findings. In the present case, we describe pulmonary side effects following the induction of general anesthesia in a child with PKU.

## 2. Case

A 10-year-old male diagnosed with PKU in the neonatal period was admitted to our center for dental treatment under general anesthesia. The patient was receiving dietary treatment for PKU, and his blood phenylalanine levels were within normal limits. His general condition was good, but he showed a lack of awareness of his environment. Due to an inability to cooperate with the dentist, general anesthesia was required for the dental treatment. No pathology was detected in the preoperative evaluation. The patient had been anesthetized twice under deep sedation (tooth extraction and circumcision) and had not experienced any problems. General anesthesia was induced with propofol (2 mg/kg), fentanyl (1 mg/kg), and vecuronium (0.1 mg/kg), administered intravenously. For maintenance of anesthesia, 2% sevoflurane and a mixture of 50% oxygen and 50% air were used. The patient's vital signs were stable. Immediately after intubation, his airway pressure (45-50 mmHg) increased, and breath sounds decreased. A bronchospasm was diagnosed. The inhaled bronchodilator salbutamol was administered, in addition to methylprednisolone (2 mg/kg), which was administered intravenously to the patient. Thirty minutes after intubation, the patient's airway pressure and ventilation improved. Oxygen saturation remained in the range of 98-99%, and no further decrease was observed. The patient was extubated without any problem, and the postoperative follow-up revealed no problem.

## 3. Discussion

Phenylalanine, which cannot be converted to tyrosine in PKU, undergoes transamination to pyruvate and conversion to phenylpyruvate. Phenylpyruvate accumulates in the blood and tissues and is excreted by urine. The metabolite phenylpyruvate results in urine and body fluids having a musty smell. In excessive amounts, the accumulated phenylalanine in the blood competes with other amino acids to pass the blood-brain barrier and can lead to a reduction of metabolites in the brain. This can result in impaired brain development and defective myelination, which can cause epileptic seizures. Phenylalanine inhibits the enzymatic synthesis of serotonin in the brain. The resulting low levels of serotonin may be the cause of the mental retardation in PKU patients. In addition, it has been suggested that a chronic lack of glutamine due to the excessive use of glutamine in the formation of phenylglutamine may be a direct cause of brain injury in PKU (Ney et al., 2014).

The accumulation of phenylalanine in non brain tissues and the decreased production of tyrosine can cause other clinical symptoms. Increased levels of phenylalanine in body fluids may reduce the amount of tyrosine, as well as that of other amino acids, in body

fluids by inhibiting the absorption of these amino acids from the gastrointestinal tract and their reabsorption from the kidneys (Giovannini et al., 2007).

Catecholamines and melanin are synthesized via a series of reactions initiated by tyrosine 3,4-dihydroxyphenylalanine hydroxylation. Thyroxine, which is synthesized by iodination of tyrosine residues, serves as the precursor of thyroid hormone (Scriver, 2007). Thus, in the absence of tyrosine, the synthesis of epinephrine, melanin and thyroxine can be reduced.

Clinical symptoms associated with deficiency of epinephrine, thyroxine and melanin can be expected in PKU. According to the literature, psychiatric symptoms are particularly common in PKU patients due to a lack of serotonin and catecholamine (Bilder et al., 2013). We thought it might be a catecholamine deficiency due to a lack of tyrosine in this case. We emphasized the hypothesis that the low level of catecholamine would be cause of experienced bronchospasm. But there are no studies in the present literature on non-neurological symptoms associated with decreased catecholamine synthesis in patients with PKU. In the present case, we described a severe bronchospasm in a child with PKU during general anesthesia. A review of the literature did not reveal any other studies on lung problems in patients with PKU.

Some peptides are known to be effective especially in airway inflammation and hyper-responsiveness resulting from infections and allergies. Dinh et al. (2005) showed that the expression of tachykinin peptides was increased in a mouse model of allergic airway inflammation. They reported that these peptides may play a role in the pathogenesis of airway diseases. There are very few studies on sympathetic neurons and their transmitters in allergic airway inflammation. In one recent study of a mouse model of allergic airway inflammation, the authors reported that the neuropeptides catecholamine and tyrosine were involved in sympathetic-adrenergic control and that the expression of these neuropeptides did not increase after allergen exposure (Dinh et al., 2004). They stated that it was not possible to completely exclude a role for these proteins in the pathogenesis of allergic airway inflammation (de Jongste et al., 1991). New studies are needed to confirm whether the bronchospasm that occurred in this case was due to a lack of catecholamine induced by PKU.

## 4. Conclusion

A link between a deficiency of catecholamines, which are required for neuronal and hormonal control, and pulmonary findings in PKU can be established with clinical and experimental studies. Further researches are needed on the potential effects of tyrosine deficiency in patients with PKU in the different organs of the body.

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