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Phenylketonuria Associated Early Onset Parkinsonism: A Case of Rapid Progression Following Dietary Nonadherence

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Abstract

Introduction: Early-onset Parkinsonism is a rare complication of phenylketonuria (PKU), a metabolic disorder marked by elevated phenylalanine and reduced tyrosine levels. This biochemical imbalance leads to dopamine deficiency in the basal ganglia, contributing to

Parkinsonian symptoms. Management requires strict dietary control and regular follow-up.

Methods: The data was collected on a case from medical reports accessible at Simon Khechinashvili University Hospital.

Results: The report is regarding a 22 year old male presenting with rapidly progressing Parkinsonian symptoms associated with PKU following dietary non adherence.

Conclusion: The following case illustrates a rare but significant association between late diagnosed, poorly controlled PKU and early onset Parkinsonism. The patient manifested rapidly progressive Parkinsonism with extrapyramidal symptoms such as tremors, oligobradykinesia, rigidity and pyramidal symptoms such as spasticity, along with basal ganglia-cortical circuit dysfunction due to metabolic imbalance which likely led to cognitive impairment. Lifelong adherence to dietary restrictions and regular neurologic monitoring are essential to prevent and potentially reverse neurological decline.

Keywords: Phenylketonuria, Parkinsonism, Dopamine, Tremors, Cognitive impairment.

Introduction

Manifestation of early onset Parkinsonism associated with PKU is a considerably rare phenomenon that occurs worldwide. PKU is a rare inherited metabolic disorder characterized by deficiency of the enzyme phenylalanine hydroxylase, which impairs the conversion of phenylalanine to tyrosine [1]. High phenylalanine levels and low tyrosine levels disrupt several neurotransmitter pathways, particularly dopamine synthesis since tyrosine plays a precursor [1,2]. Dopamine plays a major role in motor function regulation through basal ganglia. Tyrosine deficiency leads to low dopamine production in basal ganglia which contributes to extrapyramidal manifestations including Parkinsonism [6]. PKU is primarily known for its neurodevelopmental consequences such as intellectual disability, seizures and behavioral abnormalities in untreated individuals. Early treated individuals still may experience some late onset neurological symptoms [2,4]. One of the less commonly reported but clinically significant complications is early onset Parkinsonism with chronic dopamine deficiency and structural brain changes including white matter abnormalities. While there is numerous research based on PKU, Parkinsonism associated with PKU is yet to be as widely researched. Patients should follow strict dietary restrictions and do regular follow-ups to avoid complications [3,5].

Case Report

This case involves a 22 year old male who presented with tremors. The patient was diagnosed with phenylketonuria at age 1 after the onset of seizures. Patient was prescribed valproate, after which the seizures did not recur. The patient was also on a protein restricted diet which he discontinued at age 15. The tremors began afterwards, initially on the left lower limb and later progressed throughout the body. Initial management included levodopa and carbidopa combinations, a MAO-B inhibitor and a beta blocker. However, the tremors persisted. The patient remains conscious with normal cranial nerve function and sensory function, but his MoCA score was 10 which indicates severe cognitive impairment. No development delay was observed. Parkinsonism is now apparent in the patient, with spastic paraparesis of lower limbs and mild generalized oligobradykinesia. Furthermore the patient displays lead pipe rigidity with cogwheel phenomenon, postural tremor, resting tremor and action tremor on all four limbs and head. An MRI of the brain suggested a mild left periventricular hyperintensity.

Ongoing management for the patient now consists of levodopa and benserazide combination (madopar) and dietotherapy.

Discussion

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder caused by the deficiency of the enzyme phenylalanine hydroxylase, which converts phenylalanine into tyrosine [1]. As a result, phenylalanine accumulates in the body and tyrosine levels decrease. Tyrosine is a precursor for

dopamine synthesis, thereby its deficiency leads to reduced dopamine production in the basal ganglia [1,6]. Dopamine deficiency in the direct and indirect pathways affects areas like the substantia nigra and striatum, which can result in net inhibition and reduced activation of cortical motor areas [6]. This leads to the characteristic features of Parkinson's disease, such as bradykinesia, rigidity, and tremors [1]. Additionally, elevated phenylalanine levels may exert direct neurotoxic effects, impairing neurotransmitter function and brain development, especially if not treated early in life [2,4].

Although the patient was treated earlier, the dietary noncompliance in adolescence led to increased phenylalanine levels and persistent tyrosine deficiency [3]. This disrupted the dopamine synthesis abruptly, in the nigrostriatal tract and affected the proper functioning of the dopamine pathways, resulting in early onset Parkinsonism [6]. In typical Parkinson's disease, the brain can compensate for the gradual dopamine loss over the years. In contrast, Parkinsonism associated with metabolic disruption in PKU is more acute. And so, the brain has no room to adapt [6]. The patient therefore showed manifestations such resting, postural, and action tremors, lead-pipe rigidity, cogwheel phenomenon, and generalized oligobradykinesia, in a rapidly progressive manner.

Prolonged metabolic imbalance in PKU with high phenylalanine levels potentially can cause direct irreversible neurotoxicity leading to progressive neuronal damage 1,2]. The patient's history of seizures suggests early brain vulnerability as well. MRI scans showing white matter changes may point towards disrupted cortico-subcortical circuits contributing to decreased motor function [5]. The severe cognitive impairment (MoCA 10) reflects widespread brain dysfunction [2,4].

Persistence of the condition following initial treatment with levodopa, carbidopa, a MAO-B inhibitor, and a beta-blocker suggests that Parkinsonism in PKU may be less responsive to standard dopaminergic therapies [6]. While levodopa, carbidopa, and MAO-B inhibitors target dopamine pathways, their effect on the patient may be unsatisfactory if underlying dopamine synthesis remains impaired—due to a lack of precursor availability (tyrosine) and white matter damage [3].The definitive management therefore should be directed towards managing the underlying PKU. Lifelong dietotherapy with a protein restricted diet is critical to avoid progression and potential reversal of the condition [1,3]. Dopamine precursors like levodopa, tyrosine supplements can also be used alongside the strict diet to increase the dopamine reserves and repair the altered dopamine pathways [6].

Further research and case documentation is critical to better understand the spectrum and mechanisms of Parkinsonian symptoms in PKU, particularly in populations where dietary adherence may wane in adolescence or adulthood [4]. This case highlights that initial stability with treatment alone may not be sufficient; lifelong adherence to dietary therapy and regular neurologic monitoring are essential to prevent neurodegenerative conditions [3,4]. Additionally, this necessitates that clinicians remain vigilant for neurological complications in adult PKU patients, specifically those with dietary relaxes, and to consider metabolic causes in early-onset Parkinsonism [5].

Prognosis and Outcome

The prognosis in this case is uncertain due to chronic metabolic imbalance and delayed resumption of dietary therapy [4]. Even though patients initially achieved seizure control in childhood,

discontinuation of protein restricted diet during adolescence led to sustained elevation of phenylalanine and dopamine deficiency which resulted in development of early onset of Parkinsonism with pyramidal and extrapyramidal manifestations of severe cognitive impairment [1,2,4].

Even though the patient received levodopa, MAO-B inhibitors and beta blockers, limited response suggests that persistent neurotransmitter synthesis deficits and underlying structural brain changes. The current management strategy combining levodopa and strict dietotherapy may help to slow the further neurological deterioration and possibly improve symptoms modestly but full recovery is highly unlikely [3,4,6]. Further progression can be prevented by lifelong dietary compliance and close neurological follow up [1,3]. Early reintroduction of a phenylalanine restricted diet will offer neuroprotective benefits [3,5]. However, the extent of reversibility of Parkinsonism is uncertain once white matter and basal ganglia has been damaged [2,4,6].

Conclusion

This case illustrates a rare but significant association between late diagnosed, poorly controlled PKU and early onset Parkinsonism. The patient manifested rapidly progressive Parkinsonism with extrapyramidal symptoms such as tremors, oligobradykinesia, rigidity and pyramidal symptoms such as spasticity. Dysfunction across basal ganglia-cortical circuits suggested by cognitive impairment and the MRI evidence of mild white matter changes, are likely secondary to chronic metabolic imbalance [4,6]. The persistent abnormality in phenylalanine, tyrosine and dopamine levels eventually led to both motor and cognitive impairment [1,2,6].

Although PKU is typically associated with cognitive and developmental delays, progressive movement disorders in early adulthood are less frequently reported. Patient's normal early development but later neurological decline emphasizes the critical role of lifelong dietary compliance even after initial stabilization. Alternatively, this highlights a critical period during adolescence when dietary adherence often wanes. The eventual motor and cognitive decline depict the insidious and cumulative nature of neurological dysfunction.

Moreover, this case underlines the necessity of early diagnosis, continuous dietary restriction, and regular neurological evaluation in PKU patients to prevent irreversible neurodegeneration and preserve their quality of life.

Strengths and Limitations

The case highlights a rare clinical phenomenon with a comprehensive pathophysiology, which is very valuable for expanding clinical awareness. It offers practical implications for care highlighting the importance of lifelong dietotherapy and regular follow ups.

However this study reports on a single patient which limits the ability to find other PKU patients with Parkinsonism in a broader population. Imaging studies only show a very brief description which limits

the ability to make comparisons with patients with typical PKU imaging patterns. Even though the report states that the initial therapy has failed, it does detail the duration, dosage or the reasons for limited response to assess the therapeutic efficacy. Additionally, serial biochemical data including plasma phenylalanine and tyrosine levels were not documented which limits the ability to correlate metabolic imbalance with clinical progression. Finally, this case reports lacks long term follow up information as well as patient's current response to ongoing therapy, cognitive or motor progress or changes in imaging over time as he was an outpatient.

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