A Case of undiagnosed parental PKU
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Abstract
We report a 76 year old male with newly diagnosed phenylketonuria (PKU). He was brought to medical attention due to episodes of slow response, forgetfulness and confusion. His primary care physician ordered a plasma phenylalanine (Phe) level, which was found to be elevated. The test was ordered driven the patient’s son has a diagnosis of PKU, which was diagnosed after abnormal newborn screening. He was then referred to the Center for Genetic and Genomic Medicine for further evaluation. Plasma amino acids, complete metabolic profile and phenylalanine hydroxylase cofactor, tetrahydrobiopterin (BH4) analysis were performed. The plasma phenylalanine level was again found to be significantly elevated and molecular analysis of the PAH gene was ordered. It was recommended that the patient have a brain MRI and neuropsychological testing. The patient was found to have two pathogenic variants in the PAH gene. As a result, he was started on a trial of KUVAN® (sapropterin dihydrochloride, BH4) therapy. Small dietary adjustments were also suggested. The brain MRI demonstrated a lifelong volume loss and white matter changes. Neuropsychological testing revealed weaknesses in working memory, processing speed, executive skills, learning and memory and visuospatial skills. Until recently, the patient has been asymptomatic. He has lived a relatively normal life, is married, has a son, retired from a 45 year career as a bus driver and following an unrestricted diet.

Background
Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism resulting from pathogenic variants in the phenylalanine hydroxylase (PAH) gene. This causes phenylalanine to accumulate in the blood and the brain, which if left untreated can result in developmental delays, microcephaly, behavioral issues and seizures (1). PKU was first discovered in 1934 by Folling who was able to identify phenyl ketones in the urine of two disabled siblings (2). The PAH defect was then isolated in 1953. The Guthrie method of phenylalanine testing from a dried blood spot on filter paper was developed in 1962. This was the beginning of newborn screening and led to early diagnosis and diet management alleviating the severe consequences of PKU being left untreated (3). Until the FDA approval of Kuvan® in 2007, treatment options were limited to a lifelong diet, low in phe, including medical foods and using supplemental large neutral amino acids to block phe from crossing the blood brain barrier. The goal for treatment, as per American College of Medical Genetics and Genomics (ACMG), is to maintain a plasma phe between 120-360 umol/L. Patients who are Kuvan® responsive show a >30% decrease in baseline Phe levels (4). The goal of this therapy is to either increase protein tolerance or bring Phe levels, that were previous out of control, into treatment range. In May 2018, the FDA approved the first enzyme replacement therapy for PKU, Palynziq® (pegvaliase) (pegvaliase). The approval is for use in patients with blood Phe >860 umol. This allows patients to have phe control, improved neurocognitive effects and unrestricted protein intake (5).

Methods
The patient was seen in our clinic for an initial evaluation following an elevated plasma amino acid result ordered by his primary care physician. A metabolic genetic, genetic counselor and registered dietitian were present for the visit. A family and medical history was taken. His usual diet was reviewed. The work up included, plasma amino acids, complete metabolic profile and phenylalanine hydroxylase cofactor (BH4) analysis. The molecular analysis of the PAH gene was ordered following an elevated repeat plasma phenylalanine level. A referral was then made for a neuropsychology evaluation and a brain MRI. Filter papers from the State of New Jersey Newborn Screening program were provided to the family for monthly phenylalanine and tyrosine level checks. Upon follow up of the initial visit, a treatment plan was discussed. The process was initiated for the insurance approval of Kuvan®. sapropterin dihydrochloride. Kuvan was started on 11/21/19 at the recommended dose of 20 mg/kg/day. The patient was kept on an unrestricted diet.

Results
Molecular analysis resulted in two heterozygous pathogenic variants in PAH associated with autosomal recessive hyperphenylalaninemia, c.612T>G and c.782G>A. The phenylalanine hydroxylase cofactor (BH4) analysis showed normal levels. The patient’s initial phenylalanine tested was 1467.8 umol/L. Monthly levels checked via filter paper can be seen below in Figure 2. A brain MRI was performed without contrast revealing volume loss, while matter changes and degenerative disease. A comprehensive neuropsychological evaluation was performed to establish a baseline of the patient’s cognitive function. Based on the results in Figure 2. the patients Full Scale IQ is average. However, his Index scores varied from one category to another. Based on the above further evaluation was needed to fully understand his strengths and weaknesses.

Discussion
Untreated PKU has always been thought to result in severe neurological outcomes including, intellectual disability, microcephaly, developmental and behavioral issues and seizures. In addition, an IQ of 40 or lower at 1 year of age can also be seen. The “unusual” PKU patient is described as one with a relatively normal neurocognitive result despite having uncontrolled plasma phe levels (6, 7). The question remains, how can a patient with untreated PKU escape the devastating sequelae that are classically described. Theories presented when analyzing other “unusual cases” are lower vulnerability to phe crossing the blood brain barrier or some type of mechanism in the metabolic pathway of the brain preventing a response to the high phe levels. Although these patients seem to have somehow been protected from early child issues with intellect, they have effects to executive function, neurological, psychological and social issues later in life (6, 7).

The case presented is an example of the above “unusual” PKU patient. Despite having a diagnosed phe level of <1400 umol/L, first discovered at the age of 74 years, he lived a relatively normal life. He was able to complete school, marry and have a family. He performed a job for 45 years that required a high level of executive function, driving a commercial bus. His IQ remained average, but began to have episodes of slow response, forgetfulness, confusion and tremor later in his adult life.

Diet therapy for PKU is extremely difficult to adhere to especially as patients get older. ACMG guidelines include that therapy for PKU should not only aim to lower phe levels, but also to improve quality of life (5). With these goals in mind, Kuvan® was the best choice. A lower phe and reported increase in clarity and memory were able to be obtained with minimal impact to lifestyle. Further evaluation of these “unusual” PKU patients if needed to assess the best treatment approaches and outcomes.

References