

ADHD and PKU

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Several years ago in this newsletter (Fall 2002), I wrote an article that described what we knew about the relationship between PKU and attention-deficit hyperactivity disorder (ADHD). At that time, I concluded that more research was needed to further investigate this relationship. In the last 5 years, a great deal of research has investigated this topic. I will aim to summarize the research with a specific focus on practical implications for parents. Before considering the research, I will begin with a quick overview of ADHD.

ADHD Basics

ADHD affects 3–5% of individuals worldwide and is characterized by symptoms of inattention, impulsivity, and/or hyperactivity. These symptoms begin in childhood and cause academic, social, and functional impairments. There are currently three subtypes of ADHD: (1) individuals with only attention deficits, called the Primarily Inattentive type (~20–25% of the ADHD population). In previous years, ADHD-Primarily Inattentive type was called ADD and you may still hear this term used; (2) individuals with only hyperactivity and impulsivity, termed the Primarily Hyperactive/Impulsive type (< 5%); and (3) individuals with inattention and overactivity/impulsivity, labeled the Combined type (70–80%). ADHD frequently co-occurs with other psychiatric conditions, especially angry, disobedient behaviors (called oppositional defiant disorder), depression, and anxiety disorders.

Diagnosis of ADHD must not be based merely on the presence of the required number of symptoms; not all inattention is ADHD. (Please see table, page 5, for complete ADHD diagnostic criterion.) In fact, inattention is one of the most non-specific symptoms and is observed in multiple psychiatric conditions including depression and anxiety. It also is a completely normal phenomenon to have lapses in attention as long as these symptoms of inattention do not cause functional impairments (for example., losing your job or struggling in school because you cannot focus). Thus, just because a person is inattentive does not necessarily mean he or she has an attention disorder.

Symptom Overlap

Symptomatically, PKU shares much in common with ADHD. Within the last 5 years, there have been multiple research studies suggesting ADHD symptoms such as inattention, disorganization, and impulsivity are relatively common in individuals with PKU. While it remains controversial if individuals with PKU have ADHD, the symptom overlap between ADHD and PKU is relatively well established.

Studies also have suggested that individuals with ADHD as well as those with PKU share other similarities. For example, larger “response time” variability has been reported in both the ADHD and PKU literatures. This means individuals with ADHD as well as those with PKU are inconsistent in their response patterns, sometimes responding too quickly and other times responding too slowly. Difficulties sustaining attention also are commonly reported; maintaining attention over time can be difficult for both populations. Slowed general processing speed is common in PKU and the Inattentive subtype of ADHD. Individuals with PKU as well as those with ADHD—Inattentive type are often described as cognitively “sluggish.”

Much research also suggests higher phenylalanine levels are associated with higher levels of inattentive symptoms. Thus, it remains unclear whether the higher ADHD symptom expression in PKU represents “true” ADHD or rather is a “medical mimic.” Thus, before assuming that a child (or adult) with PKU has ADHD, it seems important to first rule out elevated phenylalanine levels as the cause of the ADHD symptoms.

Similarly, stimulant medications such as Ritalin and Adderall are used in the PKU population at elevated rates compared to both typically developing children as well as children with diabetes, another chronic medical condition. Nonetheless, phenylalanine levels in those with PKU who are prescribed Ritalin are higher than those who are not prescribed Ritalin. Again, this suggests that those with higher phenylalanine levels may have more robust ADHD symptoms. Alternatively, it could imply that stimulant medications are being employed in lieu of strict dietary adherence. Either way, data suggest that stimulant medications and high phenylalanine levels often occur together.

Despite these numerous similarities, not all (or possibly even a majority of) individuals with PKU are inattentive and/or

impulsive. Thus, it is difficult to uniformly assert that PKU causes ADHD. Nonetheless, the rates of ADHD in PKU are still above the ADHD population prevalence rate of 3–5%, implying that PKU may somehow be associated with an increased risk for ADHD.

The timing of the exposure to elevated levels of phenylalanine also appears critical to assess. Several years ago, Dr. Susan Waisbren and I studied three groups of children: 1. Children with PKU (n = 46); 2. Children born to mothers with PKU (n = 15); and 3. Control participants (non-hyperphenylalanemic siblings of children with PKU) (n = 18). None of the participants with PKU were taking any psychopharmacological medications, despite six participants with PKU having been previously diagnosed with ADHD. All participants with PKU were, and had consistently been, on a phenylalanine-restricted dietary treatment protocol at the time of participation. The phenylalanine levels obtained immediately (less than 20 minutes) following participation ranged from 0.9-22.8 mg/dl (54-1368 micromol/L (average=8.1 mg/dl or 480 micromol/L).

Our findings suggested that the type of ADHD symptoms expressed depended on exposure timing: prenatal exposure (as is seen in Maternal PKU) was associated with a higher likelihood of expressing hyperactive/impulsive symptoms; postnatal exposure (as occurs in PKU) was associated with a higher likelihood of expressing inattentive symptoms. This toxicity was dose-dependent and higher levels of phenylalanine appear more detrimental.

Independent Condition or Variable Manifestations of a Single Problem?

Rather than accepting that ADHD is a valid disorder in PKU, some in the field have proposed that difficulties using executive functions are a common element between ADHD and PKU. Executive functions represent an “umbrella construct” that includes a collection of interrelated functions that are responsible for problem-solving behavior. Executive functions include the ability to formulate goals; to focus and sustain attention; to inhibit impulsive responses; to generate effective and efficient problem solving, organizational, and learning strategies; and to monitor and correct one’s performance when necessary. There are many studies that suggest individuals with ADHD as well as those with PKU both have difficulties using their executive functions. Rather than having ADHD, it is the deficits in executive functioning that cause youth with PKU to appear as if they have ADHD.

Those in the field who forward this notion argue that ADHD and PKU are both considered to be “prefrontal” disorders and are regarded as being associated with a deficiency of the neurotransmitter, dopamine. (The prefrontal cortex area is the most forward area of our brain and sits just behind our eyes.) The prefrontal area of the brain is the area that is most involved with executive functioning and is exquisitely sensitive to dopamine reductions, which can occur in the face of high blood phe levels. Thus, lower levels of dopamine are particularly problematic to the prefrontal area.

Difficulties in executive functioning are observed in multiple medical (for example, PKU, diabetes, cancer) and psychiatric conditions (for example, ADHD). It therefore seems unwarranted to associate executive functions with any specific pathology any more than it would be justified to claim that inattention falls within the sole province of ADHD. Thus, rather than assuming that individuals with PKU have ADHD as an independent condition, some have proposed that it may be more fruitful to consider that difficulties using executive functions are a common element between ADHD and PKU in the same way a “fever” is associated with pathology, but not in a way that is disorder-specific.

Practical Information for Parents

The research reviewed above suggests many overlaps between ADHD and PKU, especially in the context of poor dietary adherence. The research also suggests a dose: response relationship. That is, poorer PKU dietary adherence leads to higher ADHD symptoms. Finally, research suggests that the timing of exposure to elevated levels of phenylalanine is important to consider; earlier exposure leads to a higher likelihood of hyperactive/impulsive symptoms while later exposure leads to more inattentive symptoms.

Parents of children with PKU may sometimes get conflicting advice about ADHD and ADHD treatment options. A clear implication that arises from the research to-date suggests that if ADHD symptoms (a) persist after phenylalanine levels are well-controlled and (b) the ADHD symptoms are impairing the individual’s functioning, it may be beneficial for parents to consider standard ADHD treatments. Standard ADHD treatments include the use of stimulant medications which work in part by raising dopamine levels in the prefrontal cortex. Behavioral therapies also are included in an ADHD treatment package. These behavioral therapies aim to improve both the frequency and consistency of self-management behaviors in children with ADHD, largely by training parents how best to manage the child’s behaviors.

Unfortunately, as is common among youths with complicated clinical pictures, ADHD in PKU may be diagnosed late (or not diagnosed at all). Should ADHD symptoms persist in the presence of well controlled phenylalanine levels, ADHD should be entertained as a diagnostic possibility. Although adherence with the daily complex regimen for managing PKU is challenging for any individual, the tasks may be especially daunting for someone with co-occurring ADHD. Individuals with ADHD have difficulty with organization, planning, forgetfulness, and impulsivity that may directly impede their ability to monitor and regulate phenylalanine levels. By not treating ADHD, the risk for poor treatment adherence rises.

Finally, direct involvement with school personnel is critical for children with PKU and ADHD. Direct communication with school personnel and effectively advocating for your child in the school setting are central to both PKU and ADHD management.

Summary

While most clinicians agree that ADHD symptoms are relatively common in individuals with PKU, the issue of diagnosing ADHD in those with PKU remains controversial. People on all sides of the controversy acknowledge the significance of accurate diagnoses. Under-diagnosis of ADHD may lead to under-treatment, or the provision of appropriate medical and psychological services to only the most severe patients. Over-diagnosis (false positives; for example, diagnosing ADHD in a child with PKU who does not really have ADHD) has its own disadvantages, including unnecessarily treating with stimulants.

Criterion E of the DSM-IV (see table at right), the diagnostic manual used to guide mental health professionals in making a psychiatric diagnosis, states that in order to make a diagnosis of ADHD, the ADHD symptoms "cannot be better accounted for by another mental disorder." While PKU is clearly not a mental disorder, the underlying principle of excluding other causes for the ADHD symptoms should apply in PKU. If improved metabolic control decreases ADHD symptoms, it becomes very difficult to diagnose ADHD as an independent condition.

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