Section A -Research paper

Psychosocial Dysfunction in Phenylketonuria Patients: Review Article

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Abstract:

Psychological and psychiatric problems are well documented across the lifespan of individuals with early-treated phenylketonuria (PKU). Early-treated children and adolescents tend to display attentional problems, school problems, lower achievement motivation, decreased social competence, decreased autonomy, and low-self-esteem. As they enter adulthood, early-treated individuals may carry forward low self-esteem and lack of autonomy but also tend to develop depressed mood, generalized anxiety, phobias, decreased positive emotions, social maturity deficits, and social isolation. The correlation between level of metabolic control and severity of symptoms suggests a biological basis of psychiatric dysfunction. Additionally, psychosocial factors such as the burden of living with a chronic illness may contribute to psychological and psychiatric outcomes in PKU. The lack of a PKU-specific psychiatric phenotype combined with the observation that not everyone with PKU is affected highlights the complexity of the problem. More research on psychiatric and psychological outcomes in PKU is required. Of particular importance is the routine monitoring of emotional, behavioral, and psychosocial symptoms in individuals with this metabolic disorder. Longitudinal studies are required to evaluate the impact of new and emerging therapies on psychiatric and psychosocial functioning in PKU. Unidentified or untreated emotional and behavioral symptoms may have a significant, lifelong impact on the quality of life and social status of patients.

Keywords: Psychosocial Dysfunction, psychiatric, Phenylketonuria.

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Introduction:

PKU is considered one of the most common biochemical causes of mental disabilities as the accumulation of excess PHE in the brain cells leads to severe neurodevelopmental delay in untreated patients usually in the form of intellectual disabilities , seizures and growth retardation with a wide range of psychological disorders and cognitive abnormalities (1).

it has been established that neuropsychological dysfunctions in PKU patients are related to PHA levels through different life stages including current PHE level , life time PHE levels variations in PHE levels and PHE/TYR ratio (2).

the primary cognitive dysfunction often seen among untreated PKU patients is slow processing reflecting slow action potential traveling along myelinated nerves denoting the theory of toxic effect of PHE on oligodendrocytes in central nervous system rather than Schwan cells in peripheral nerves as discussed in chapter one (3).

Psychiatric disorders:

typically , untreated patients of PKU have been reported to show a variety of psychological signs and symptoms dating back to the earliest description of the disease by Følling in the beginning of the bast century ranging from shy , angry, agitated , irritable with affection symptoms including depression and euphoria up to severe forms of psychosis ,hallucinations ,delusions, catatonia and intellectual disabilities (4).

while modern literature about this subject denote marked autistic and psychotic spectrum with aggressive and agitated behavior with difficult management of these disorders in specialized institutes (5).

Children, adolescents, and adults with PKU can display disturbed emotional and behavioral functioning with evidence of a heterogeneous range of phenotypes, as summarized in the following table :

Table (1): phenotypes of emotional and social problems in PKU patients (5).

untreated	**Early treated children and adolescents**	**Early treated adults**
Psychotic symptoms	Attention problems	Depressed mood
Autistic behavior	School problems	Social isolation
Hyperactivity	Low achievement motivation	Generalized anxiety
aggression	Low self esteem	Phobias
anxiety	Low social competence	Social maturity defects
Depressed mood	Decreased autonomy	Decreased positive emotions

Depression:

To be diagnosed with a major depressive disorder, according to the childhood depression rating scale (CDRC)the child should show at least one of the following two major criteria for most of the day, for most days of the week, in the period of same 2 weeks:

Table (2) diagnostic criteria for major depressive disorder (6).

1- Continuous feeling of sadness or irritability
2- Loss of interest in all or most of the previously enjoyed activities
3- Plus , at least one of the following criteria :
1- Loss of hope or feeling helpless 2- Low self esteem
3- Feeling inadequate
4- Excessive or unexplained feeling of guilt
5-Troubles making healthy relations or social withdrawal 6-Sleeping abnormalities either insomnia or hypersomnia
7-Appetite and weight changes
8- Loss of energy
9- Deteriorating school performance and troubles with concentration
10- Increased fear of failure or rejection
11- Difficulty making decisions
12-Frequent complaining of headache , fatigue or stomachaches without physical cause
13-Frequent thoughts of death
14-Suicidal ideas

Prevalence of depression is significantly higher among PKU patients of all age groups in comparison to normal population according to a retrospective cohort study showing the incidence of clinical depression being 18 % among PKU patients subdivided into 12% in early treated patients and 35% in late treated patients in comparison to 11% in general population (7).
The mechanism by which clinical depression occurs in PKU patients is thought to be multifactorial including neurochemical ,neurohumoral and neuroinflammatory processes in presence of environmental factors such as strict dietary adherence and peer pressure (8).
However , it is strongly suggested that depressive symptoms in PKU patients is related to the defective monoamine transmitters as dopamine , serotonin and norepinephrine resulting from the hyperphenylalaninemia which is supported by a study showing that higher levels of PHE is related to acutely depressed mode (9).
Most antidepressive medications act by restoring monoaminergic networks that project to the frontal cortex and cortico-limbic system particularly by modifying the gene expression and synaptic neuroplasticity improving the clinal symptoms of depression (10).

Anxiety:

Children with generalized anxiety disorder may experience somatic symptoms such as shortness of breath, rapid heartbeat, sweating, nausea or diarrhea, frequent urination, cold and clammy hands, dry mouth, trouble swallowing, or a "lump in the throat.", headache ,stomach pain, Problems with muscle tension
including trembling, twitching, a shaky feeling, and muscle soreness or pain in absence of organic cause of these symptoms (11).
For children, anxiety is associated with one (or more) of the following six symptoms (with at least some symptoms reported or more days than not for the past 6 months):

Table (3) diagnostic criteria for anxiety disorders (12).

1-Restlessness or feeling on edge
2-easy fatiguability
3-Difficulty concentrating or mind block
4-Irritability
5-Muscle tension
6-Sleep disturbance (difficulty falling or staying asleep, or restlessness, unsatisfying sleep)

Anxiety is one of the most commonly reported psychiatric symptoms in both pediatric and adolescent PKU patients with significantly higher rates (15.6%) than those of general population (9.2 %) with heterogeneous clinical presentations strongly related to plasma PHE levels and age of initiation of treatment (13).

A wide range of anxiety disorders have been demonstrated among PKU patients including generalized anxiety disorder, obsessive compulsive disorders , specific phobias and panic disorders (14).

Anxiety disorders have been generally associated with low serotonin levels in the brain resulting from different alterations in serotonin regulatory system including the gene encoding for CNS – tryptophan hydroxylase (TPH2) and polymorphism of

serotonin transporter gene (SERT) and giving the fact that high levels of PHE in PKU is associated with low serotonin levels , this can explain the higher incidence of anxiety disorders among PKU patients (15).

Prevalence of anxiety disorders differs greatly among early and late treated PKU patients as typically late treated patients tend to show more externalizing symptoms as aggression, agitation and mental delay where as early treated patients with restricted PHE diet tend more to show internalizing symptoms as anxiety , low self esteem and social withdrawal (16).

There is an obviously noted relation between PHE levels and frequency of anxiety disorders as recent studies stated that adolescents who have lower PHE levels are less likely to suffer from anxiety as well as improvement of symptoms in patients when they return to PHE restricted diet (17).

It is important to keep in mind that strict following of restricted diet for long periods of time can represent a psychological burden on patients and their families leading to higher rates of anxiety disorders (18).

Treatment with selective serotonin reuptake inhibitors may be useful particularly in patients who fail to keep low PHE levels (19).

Psychosis:

childhood onset schizophrenia is generally a rare disease with incidence of about 1% among general population diagnosed by onset of symptoms before age of 13 years ,to be diagnosed with childhood onset schizophrenia , patient must fulfill at least 2 of the following 5 criteria for at least one month according to DSM5 :

Table (4) diagnostic criteria for schizophrenia according to DSM 5 (20).

1-dellusions
2-Hallucinations
3-Disorganized speech
4-Grossly disorganized or catatonic behavior
5 Negative symptoms

While schizophrenia is not considered among the most common neuropsychiatric disorders in PKU patients, it still occurs in higher rates in those patients compared to general population (21).

Modern literature suggests an association between PKU and schizophrenia polymorphism implying a genetic explanation of this relation while a group of chronic schizophrenic patients

under medical treatment was also found to have decreased Phe levels compared to controls, supporting the role of phenylalanine imbalance in schizophrenia (22).

Attention deficit hyperactivity disorder (ADHD):

Attention deficit hyperactivity disorder is a multifactorial developmental neuropsychiatric disorder based on genetic predisposition and neurobiological dysfunction with a relatively high prevalence of 3-5 % among general pediatric population (23).
according to DSM-IV symptoms of ADHD are classified into 2 groups : inattention and hyperactivity or impulsive symptoms which categorize 3 subtypes of the disease : predominant hyperactive subtype (5%) , predominantly inattentive subtype(25-30%) and combined subtype(65-70%) and the diagnosis of ADHD is made by presence of at least six of inattentive symptoms and / or six of impulsive symptoms as following:

Table (5) diagnostic criteria for ADHD according to DSM 5 (24).

inattentive symptoms:
1-Often fails to pay full attention to details or makes careless mistakes in schoolwork, work, or other activities
2- Often struggles to keep attention to tasks or play activities
3- Often does not seem to listen when someone speaks to him directly
4- Often does not follow instructions and fails to finish schoolwork or duties in the workplace (not due to oppositional behavior or misunderstanding of instructions)
5-Often has difficulty organizing tasks and activities
6-Often avoids, dislikes, or is reluctant to doing tasks that require continuous mental effort (such as schoolwork or homework)
7- Often loses things necessary for tasks or activities as toys, school assignments, pencils, books, or tools
8-Is often easily distracted by external stimuli
9- often with forgetful behavior in daily activities
Impulsive / hyperactive symptoms:
A-Hyperactivity:
1- Often seems restless with hands or feet or squirms in seat
2- Often leaves seat in classroom or in other situations when staying seated is expected
3- Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents, may be limited to subjective feelings of restlessness)
4-Often finds it difficult to play or get engaged in free time activities quietly
5- Is often “on the go” or often acts as if “driven by a motor”

6-Often talks excessively

B-Impulsivity

7- Often rushing to answers before questions have been completed

8- Often has difficulty awaiting for his turn

9- Often interrupts or intrudes on others

These symptoms must be interfering with social, academic, or occupational functioning and the symptoms must not occur exclusively during the course of a another developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder) (25).

A study compared 46 children with early and continuously treated PKU to a healthy control group showed that the PKU group had higher ADHD prevalence with positive relationship between PHE levels and ADHD symptoms (26).

The association between PKU and ADHD can be partially explained by the hypodopaminergic theory as in both PKU and ADHD patients, this hypodopaminergic state is particularly noticed in the prefrontal cortex which requires precise neurochemical balance to perform attentive functions properly as demonstrated in a study conducted over 4 years on the executive functions of a group of early treated PKU with PHE levels three to five times normal (despite
early dietary restriction), their performance was defective regarding working memory and inhibition that were dependent on the functioning of the dorsolateral prefrontal cortex and the correlation of these findings with PHE levels implies that dopamine dysfunction was the underlying problem (27).

Given the high sensitivity of the prefrontal cortex to low levels of dopamine, it is not surprising that this area is disproportionally affected by the sequelae of even mild elevations of PHE , and this provides a likely mechanism for the increased rates of ADHD in PKU (28).

cognition in PKU :

cognitive outcomes in early treated PKU :

a meta-analysis of studies conducted on children and adolescent with PKU concluded that children with early and continuously treated PKU will score average results in IQ test despite they may be less than their genetically related control subjects (29).

For the majority of adults that commenced treatment shortly after birth, individuals generally fall within the normal range of general cognitive ability, have professional and educational achievements similar to their non-PKU siblings, and are able to live independent and productive lives (30).

However, there are some individuals that continue to demonstrate neuropsychological, social, and behavioral difficulties throughout their adult lives ,such challenges can impact on education and training, employment, relationships, emotional wellbeing, and quality of life (31).

However ,the relationship between PHE levels and cognition across the lifespan was variable, with no definitive linear pattern of association found. This was thought to reflect a number of core challenges in studying cognition in PKU Including high heterogeneity in the nature of study samples, resulting in large variability in phenylalanine levels, as well as wide variation in the type and sensitivity of neuropsychological measures used to assess cognitive functioning
(32).

Mild to moderate dysfunction was reported among early treated PKU patients including attention, general intelligence ,processing speed ,executive function , working memory , new learning memory , mental flexibility , planning , reasonable thinking , academic achievement , hand skills and coordination with these cognitive dysfunction markedly related to PHE levels, mostly these executive dysfunctions are highly related to white matter dysfunction as proved by MRI (33).

As a result of these difficulties , parents , teachers and even the patients of PKU themselves must be aware of the challenges they may face in both academic and social context and the additional support and counselling they may need to compensate for those cognitive dysfunctions

Cognitive outcomes in late or untreated PKU:

Untreated PKU is characterized by motor deficits, intellectual
disability, microcephaly, autism, seizures, developmental problems, behavioral issues, and a range of psychiatric symptoms (34).

Failure to implement treatment in the neonatal period causes substantial lifelong disability through the toxic effects of excess Phe exposure to the brain, in particular to myelin and dendritic projections during critical postnatal periods of neuronal development proved by MRI and histopathology of individuals with late- or never-treated PKU demonstrating diffuse cortical atrophy, hypomyelination, white matter vacuolization, and astrocytic gliosis (35).

In a retrospective study aiming to investigate the relationship between neurological complications and behavioral problems, age at diagnosis and dietary control76% were diagnosed through neonatal screening. There were 12.4% with mild PKU, 19% moderate PKU, and 68.6% classic PKU. Eighty-eight percent of patients were treated with a protein-restricted diet, and the remainder with BH4

almost all (97.7%) of the early-diagnosed patients had normal IQ, while46.3% of late diagnosed patients had intellectual disability, 28.5% were borderline, and 25% had normal IQ (36).

The severe cognitive impairments seen in untreated PKU can be partially reversed with dietary treatment in many individuals, but the prompt initiation of treatment following newborn metabolic screening remains essential for the prevention of disability and optimal neurodevelopment (37).

Social Cognition and PKU:

Social cognition is a domain of cognition involving all mental processes that underlie social interactions, and encompasses the ability to perceive, interpret, and then respond appropriately to social cues. Some basic social cognitive skills include face and emotion recognition and theory-

of-mind (the capacity to attribute and understand feelings, thoughts, and intentions to/of others) (38).

Deficits in social cognitive abilities are consistently reported in individuals with executive dysfunction, because of shared underlying neurobiology and neuroanatomy. In other disorders affecting the CNS, impairments in executive function have been correlated with deficits in communication skills and social relationships (39).

High Phe levels may in some cases result in irritability, impacting on adaptive social skills and it has been reported that quality of patients' social cognition was inversely related to recent Phe levels, and to levels between 8 and 12 years, for PKU adolescents, it was also inversely related to lifetime phenylalanine levels in adult patients, and more specifically to Phe levels up to 12 years of age with no differences observed between the BH4 and non-BH4 groups (40).

Impairments in functioning seem to be more evident among adolescents and adults with PKU, with high Phe levels during childhood and early adolescence (presumably during critical periods of development of frontal circuits subserving social cognitive functioning) seem to be of greater influence than current and recent Phe levels in PKU individuals (31).

Neuropsychological Assessment Recommendations:

There is currently no consensus regarding a standardized PKU neuropsychological battery for children or adults but the European guidelines suggest that neuropsychological assessment should occur on an "as needed" basis in

childhood, with routine evaluations at 12 and 18 years of age with correlation to changes in treatment targets for blood Phe and life changes including school transitions, living situation, and transfer to adult clinics and brain development (41).

When conducting a neuropsychological assessment in individuals with PKU, it is important for clinicians to conduct a comprehensive examination encompassing all cognitive domains and if time is limited, the domains most likely to be susceptible to high Phe levels are attention, working memory ,motor control , complex speed of processing, and executive functioning (42).

Table (6) European guidelines neuropsychological assessment recommendations (43).

Neuropsychological assessments should be conducted at 12 and 18 years in all patients
If any of the stated risk factors applies, perform (additional) neuropsychological assessment:
• Non-optimal metabolic control; <50% of the Phe levels are out of target range over a period of 6–12 months (depending on age <12 or >12 years)
• Problems at school or work
• Concerns of parents/caregivers/family/teachers
• Concern of PKU patient
• Concern of metabolic team
Cognitive domains for Inclusion

Estimation of intelligence Academic achievement Immediate, divided, and sustained attention Speed of processing Visuo-spatial functioning Verbal new learning and memory Expressive and receptive language Motor speed and coordination Executive functions: • Working memory • Inhibitory control/self-monitoring • Planning and organization • Cognitive flexibility/shifting • Verbal fluency Social cognition Psychiatric screening Psychosocial adjustment/quality of life Behavioral rating scales

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