Original paper

Diagnosis of phenylketonuria in Children with Autistic symptoms

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Abstract

Background: Autism is a behavioral syndrome with still poorly understood etiologies, nevertheless, phenylketonuria (PKU) was frequently associated with autistic symptoms, and the frequency of this association is variably reported
Aim of the study: to bear in mind the diagnosis of phenylketonuria in children presented with autistic symptoms.
Patient and methods: Patients with Autistic disorder was diagnosed according to DSM-5 diagnostic criteria, We describe fourteen patients, eight males and six female, their presentation were autistic behavior with clinical findings included hair hypopigmentation, microcephaly , mousy urine odour and/or positive family history of sibling with same condition,
Result: Autism was present in 14 (26%) of phenylketonuria cases diagnosed with same period; 12 patients had classic PKU and 2 had mild PKU, with average age 5.1 ± 2.696 , all of them are borne to related parent and they have one or more features making PKU index of suspicion.
Conclusion: The present study confirms that PKU is one of the causes of autism. Delay in the diagnosis and management of PKU, may leads to significant incidence autistic features in these patients.
Keywords: Phenylketonuria, Autism

Introduction

Historical background of PKU

The story of phenylketonuria (PKU) is the "Book of Genetic" in the world of genetic disorders. PKU was the 1st recognized cause of intellectual disability, the 1st known metabolic disorder and the 1st genetic disorder for which a treatment could prevent its most devastating effects. To read pearl Buck's heartrending description of her daughter, Carolina Grace, who had untreated PKU and to know the tragedy of untreated PKU is to appreciate the "miracle" of treatment.(1) PKU requiring therapeutic intervention to prevent neurological damage is usually diagnosed on the basis of blood phe (phenylalanine) >360µmol/l (depending on national guide lines). However, the classification of HPA and PKU is not simple. Previously, it could be based highest blood phe levels before introduction treatment. Patients with blood phe levels of 120-600 µmol/l (2-10 mg/dl) were classified as mild (non-PKU), HPA; blood phe levels of 600-1200µmol/l (10-20mg/dl) were classified as mild PKU and levels above 1200µmol/l (20 mg/dl) as" classical" PKU. However, this can only be applied when phe reaches its full potential biological value due to a longer period without treatment. Classification is not accurate when the phe level used for classification is obtained from newborn screening and may not have had time to reach highest level. Thus, classification

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must also consider the tolerance for dietary phe.[2]

Children with classic PKU untreated by a phe-restricted diet, develop sever intellectual disability, seizures, ataxia, motor deficits and behavioral problems and in these children exhibit developmental problems; which may be accompanied by aberrant behaviors including self-harm, aggression, impulsivity, and psychosis.[2]

The association between autism and PKU has important implications for understanding possible underlying factors in the development of autism. In the case of PKU, the toxic levels of Phe appear to play a significant role in the development of autism symptomatology.[3] Biogenic amines have been shown to facilitate formation of synapses in the developing brain. The accumulation of Phe in patients with PKU with lack of biogenic amines in the brain is associated with the presence of mental retardation and autism.[4] Autism is an etiologically and clinically heterogeneous group of disorders, collectively referred to as the "autism spectrum disorders" (ASDs).[5] First described in the early 1940s almost simultaneously by psychiatrists Kanner[6] in the United States and Asperger[7] in Austria.

The present study was conducted to diagnosis of phenylketonuria in children presented with autistic symptoms in pediatric neurology clinic in welfare teaching hospital, medical city campus, Baghdad, Iraq.

Patients, Materials and Methods

This is a single center descriptive cross sectional study was conducted at the pediatric neurology department and clinic at Welfare Teaching Hospital, Medical City, Baghdad, for the period from 1st February 20014 to 1st December 2016. during this period 55 patients were diagnosed to being PKU (prove by fluorescent HPLC amino acid analysis) for suspected where relies mainly on a high index of clinical suspicion warranting confirmatory testing by laboratory analysis of amino acid (AA), in addition to the basic metabolic investigation, 14 of them their initial presentation were autistic feature.

The inclusion criteria included;

1- Selected cases of patients with autistic spectrum disorder (positive family history, unusual urine odour) that their AA analyses prove to have PKU or hyperphenylaninaemia.
2- Patients diagnosed 1 year or more after birth
3- No evidence of any other systemic or metabolic diseases

Exclusion criteria; Early and continuously treated PKU patients.

Basic diagnostic investigations*;*

Up on clinical suspicion of an AA disorder, basic metabolic investigations were performed using routine methods for measurement of serum glucose, electrolyte, liver function test (aspartate aminotransferase, alanine amino transferase). Arterial blood gases, ammonia, lactate.

Ethical approval

All patients and their families were informed about the aim and suspected benefit of the study before obtaining their agreements for participation according to the medical research and ethical regulations, thus an oral consent was taken from all enrolled participants and their families. All the medical research ethics rules and instructions regarding patient's privacy, humanity and security; as well as the medical research, laboratory data and investigation results were strictly considered throughout all the steps of study.

Diagnosis*;*

Autistic disorder was diagnosed according to DSM-5 diagnostic criteria,[8] structured interviews of at least one hour each with the both parents and the child were performed, in a room equipped with play material appropriate for age level,

Phenylalanine Levels, Concurrent levels for all cases with PKU (taken directly after completion of psychological assessment) were included Based on blood Phe levels at diagnosis, there are 4 levels of PKU severity;

1- Hyperphenylalaninemia, with Phe levels that are slightly above normal range: 120-600 µmol/L (2-10 mg/dL)
2- Mild, with the lowest blood Phe levels: 600-900 µmol/L (10-15 mg/dL)
3- Moderate or variant, with blood Phe levels somewhere in the middle: 900-1200 µmol/L (15-20 mg/dL)
4- Severe or "classic" PKU, with extremely high blood Phe levels: >1200 µmol/L (20 mg/dL).[9]

Statistics

Statistical analysis and reporting of obtained data were carried out by descriptive pattern. Data were reported and presented as tables to show the frequency distribution (number and percent (N, %) of variables; also, results presented as graphs (histogram) to show the frequency distribution (number and percent (N, %) of variable.

Results

Fifty five pediatric patients were diagnosed as PKU by fluorescent HPLC, fourteen of them were initial presentation ASD symptoms enrolled in this study; patients were diagnosed according to DMS-5.

Table 1 shows the demographic data of the study, the study included 8 males (57 %) and 6 females (43%), There were positive consanguinity in all patient, distributed as 1st cousin in 11 patient (78,5%), one patient double cousin ,tow patient were far relative.

Family history of PKU for sibling with same features present in 7 patient (50%), 12 patients had classic PKU (86%) and 2 of them mild PKU (14 %).

The age at diagnosis ranged from 2 years to 12 years (mean: 5 yr.) (Table 2). Late diagnosis of PKU in studied patients is attributed to the incomplete late of screening program for PKU in Iraq.

The pku patients was classified into classical and mild according to severity. As regard clinical findings the typical PKU features (microcephaly, fair complexion) was present in 8 cases (57%), and musty urine odor was observed in 8 cases (57%), seizures were present in 3 patient (21%) ;(Table 3).

Table 1. General description of the study samples

	N	%
gender		
male	8	57
female	6	43
total	14	100
Consanguinity		
1st cousin	11	78
Double cousin	1	7
Distant cousin	2	14
Not related	0	0
total	14	100
Family history		
present	7	50
absent	7	50
total	14	100

Table 2. The Age of patients at time of diagnosis

Age	
Range	2 - 12years
mean ± SD	5.1 ± 2.696
Median	5
Mood	3

Table 3. The classification and clinical features of PKU

Classification of PKU according to phe. Level	%	
Classical PKU	12	86
Mild PKU	2	14
total	14	100
Clinical features		
Typical PKU feature	8	57
Seizure	3	21
Musty urine odor	8	57

Discussion

PKU pathology is almost restricted to the brain. The etiology of cognitive problems arising from as result of HPA is unclear, and mechanism may be involved at various levels (effect on brain protein and neurotransmitters, oxidative damage, white matter damage, impaired large neutral amino acids uptake into brain and other unknown effect).[10]

Since the description of PKU in 1934 by Fölling, several authors, mainly from the earlier medical literature, reported individuals with autism and PKU. [11and 12]

In Iraq, neonatal screening is applied recently only to capital and one province and so diagnosis of PKU depends on clinical manifestations detected by experienced physicians, leading to late diagnosis of this disease in an irreversible stage. In our study unique and different from other studies by searching for PKU in autistic patients rather than revers this rising question of whether these PKU subjects share a peculiar autistic phenotype or whether their behavior represents the evolution of autism with age, and stress the need of further controls in following years. In the present study; typical PKU features (microcephaly, fair complexion) and musty urine odor were the most frequent clinical manifestations detected in 57% of all cases therefore typical known feature not always present and diagnosis depend on high index of suspicion . Seizures were much less frequent detected in only 21%, and this is agree to some extend with Egyptian study. [13]

The association PKU- autism has been documented in present study in fourteen patients(represent 25% of PKU that diagnosed in the same period) with their initial presentation was autistic features however the frequency of this condition varies widely [14], a confinable percentage of patients with PKU having autistic symptomatology are difficult to determine, especially after introduction of treatment. In1975, Knobloch and Pasamanick[15] found 14 (21.8%) phenylketonuric individuals among 64 patients with autism diagnosed by Kanner criteria, which consider at that time overestimation and this agree with present study ,nevertheless, more recently, we found two subjects with PKU in a sample of 84 individuals with pervasive developmental disorders diagnosed by DSM-IV criteria, giving a frequency of 2.3% in the total sample comprising all PDDs [16], On the other way, Baieli et al. [14] reported 35 individuals with classic PKU late diagnosed, all with mental retardation and two (5.7%) presenting autism. The link between poor control and late diagnosis PKU and autism suggests that with

improvements in diagnosis and treatment of PKU, the association with autism will likely decrease. The association between autism in PKU has important implications for understanding possible underlying factors in the development of autism.[17] In the case of PKU, the toxic levels of phenylalanine hydroxylase appear to play a significant role in the development of autism symptomatology.[12] The one point on which all authors agree is that untreated forms of PKU can be one of the etiologies of an autistic behavior pattern. Abnormal brain development resulting from dysfunctional myelination and reduced neuronal connections with dopamine deficiency are proposed as potential etiological factors for autism.[16] In the present study, autism itself was only present in a significant percentage (25%) among the group of late-diagnosed PKU and this disagree with Baieli et al study[14] found (2.5%) and this attributed to lack of complete international program, neverthless, aconfinable percentage of patients with PKU having autistic symptomatology are difficult to determine, especially after introduction of treatment.

Conclusion

The present study is the first work to describe PKU in autistic spectrum disorder diagnosed by DSM-5 criteria.

Recommendations

1) Expanded neonatal screening for PKU is highly recommended for early detection and management.
2) Further studies are needed to answer the question of whether PKU patients have a specific autistic phenotype or whether their behavior represents the evolution of autism with age with late diagnosis.

List of Abbreviations

AA	Amino acid
ASD	Autistic spectrum disorder
HPLC	High performance liquid chromatography
IEM	Inborn error of metabolism
Phe	Phenylalanine
PKU	Phenylketonuria
PAH	Phenylalanine hydroxylase
DSM-5	Diagnostic and statistical manual of mental disorders 5th edition

Competing interests:
The authors declare that they have no competing interest

Author's contributions;
Dr. Adel A. Kareem: did the literature research, analysed the data and drafted the manuscript.
Dr. Husham Z. Hammoodi: and **Dr.Maher M. Sallih:** were involved in discussion and evaluation of the data and critically revised the manuscript and also participated in the study coordination and helped to draft the manuscript in addition to contributed clinical data. All authors read and approved the final manuscript.

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