

## The Impacts of Phenylketonuria (PKU) on Children in Sohag University Hospital-Upper Egypt

Abdelrahim A. Sadek<sup>1</sup>, Ahmed M. Emam and<sup>2</sup> Mostafa Y. Alhaggagy<sup>3</sup>

<sup>1</sup>Pediatric Neurology Unit, Department of Pediatrics, Phoniatic Unit, ENT Department<sup>2</sup> and Audiology Unit, E.N.T Department<sup>3</sup> Sohag University, Egypt.

[ahmedabout2002@yahoo.com](mailto:ahmedabout2002@yahoo.com)

**Abstract: Introduction:** Phenylketonuria (PKU) is an autosomal recessive metabolic genetic disorder characterized by a mutation in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH). The disease may present clinically with seizures, albinism (excessively fair hair and skin), and a "musty odor" to the baby's sweat and urine. In the untreated classic case, mental retardation is severe, precluding speech and toilet training. Children in this category have an IQ below 50. Seizures, common in the more severely retarded, usually start before 18 months of age and can cease spontaneously. **Aims:** To identify clinical profile and impacts of PKU on children and to promote local community to establish PKU screening practice for early diagnosis and treatment. **Patients & Methods:** Children presented to the Pediatric Department, or Pediatric Neurology Clinic, Sohag University Hospital whom diagnosis of Phenylketonuria was established based on measuring phenylalanine level in blood samples. All studied patients were subjected to thorough history, full examinations, and developmental assessment. Electroencephalography (EEG), computed tomography brain (CT scan), phoniatic and audiological evaluations. **Results:** During the period of the study we diagnosed 24 cases with phenylketonuria, the main clinical presentations were global developmental delay, hyperactive symptoms, seizures, and autistic features, C T brain showed 14 cases with atrophic changes. EEG showed 14 cases with abnormal findings as generalized epileptic discharges, focal epileptic discharges, and hipsarrhythmia. **Conclusion:** phenylketonuria still represent significant burden on children development and mental function in Upper Egypt. Global developmental delay, behavioral abnormalities, and seizures were the prominent manifestations. **Recommendations;** we recommend establishment of national screening programs and pushing it forward, immediate development of specific metabolic centers in various universities and research institutes.

[Abdelrahim A. Sadek, Ahmed M. Emam and Mostafa Y. Alhaggagy. **The Impacts of Phenylketonuria (PKU) on Children in Sohag University Hospital-Upper Egypt.** *J Am Sci* 2012;8(12):1326-1332]. (ISSN: 1545-1003). <http://www.jofamericanscience.org>. 179

**Key words:** Phenylketonuria(PKU), phenylalanine(Phe), seizures, developmental delay, Autism, hyperactivity.

### 1. Introduction

Phenylketonuria (PKU) is an autosomal recessive metabolic genetic disorder characterized by a mutation in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH), rendering it nonfunctional (**James et al.,2006**). This enzyme is necessary to metabolize the amino acid phenylalanine (Phe) to the amino acid tyrosine. When PAH activity is reduced, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which is detected in the urine (**Gonzalez et al., 2010**). The mean incidence of PKU varies widely in different human populations. In Turkey, 1 in 2600 births (the highest rate in the world) show PKU; in Ireland, 1 in 4,500 (**Guldborg et al.,1995**), 1 in 13,000 in Norway, and fewer than one in 100,000 in Finland. In the United States, about 1 in 15,000 births show classical PKU. The incidence is relatively high in Italy, China, and Yemen (**DiLella et al., 1986 & Ozalp et al., 2001 and Loeber, 2007**).

PKU is commonly included in the newborn screening panel of most countries, with varied detection techniques. Most babies in developed countries are screened for PKU soon after birth( **Mayo Clinic Staff**

,**2007**) Screening for PKU is done with bacterial inhibition assay (Guthrie test), immunoassays using fluorometric or photometric detection, or amino acid measurement using tandem mass spectrometry (MS/MS). Measurements done using MS/MS determine the concentration of Phe and the ratio of Phe to tyrosine, both of which will be elevated in PKU( **Sarafoglou et al.,2008**). If a child is not screened during the routine newborn screening test (typically performed 2 - 7 days after birth, using samples drawn by neonatal heel prick), the disease may present clinically with seizures, albinism (excessively fair hair and skin), and a "musty odor" to the baby's sweat and urine (due to phenylacetate, one of the ketones produced). In most cases, a repeat test should be done at approximately two weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed. Untreated children are normal at birth. In untreated infants, vomiting which at times projectile and irritability are frequent during the first 2 months of life. By 4 to 9 months, delayed intellectual development becomes apparent (**Partington, 1961**).

In the untreated classic case, mental retardation is severe, precluding speech and toilet training. Children in this category have an IQ below 50. Seizures, common in the more severely retarded, usually start before 18 months of age and can cease spontaneously. During infancy, they often take the form of infantile spasms, later changing into tonic-clonic attacks. The untreated phenylketonuric child is blond and blue-eyed, with normal and often pleasant features. The skin is rough and dry, sometimes with eczema. A peculiar musty odor, attributable to phenylacetic acid, can suggest the diagnosis. Significant neurologic abnormalities are rare, although hyperactivity and autistic features are not unusual. Microcephaly may be present as well as a mild increase in muscle tone, particularly in the lower extremities. A fine, irregular tremor of the outstretched hands is seen in approximately 30% of the patients. Parkinsonian-like extrapyramidal symptoms also have been encountered. The plantar response is often extensor ( **MacLeod et al., 1983**).

A variety of electroencephalographic (EEG) abnormalities has been found, but hypersarrhythmic patterns, recorded even in the absence of seizures, and single and multiple foci of spike and polyspike discharges are the most common ( **Gross et al., 1981**). MRI is abnormal in almost every patient, regardless of when treatment was initiated. On T2-weighted imaging, one sees increased signal in the periventricular and subcortical white matter of the posterior hemispheres. Increased signal can extend to involve the deep white matter of the posterior hemispheres and the anterior hemispheres. No signal abnormalities are seen in brainstem, cerebellum, or cortex, although cortical atrophy may be present ( **Pearson et al., 1990 and Cleary et al., 1995**). The severity of the abnormality is unrelated to the patient's IQ but is significantly associated with the phenylalanine level at the time of imaging. In adult patients with PKU who had come off their diets, resumption of dietary treatment can improve MRI abnormalities within. In contrast, affected children who are detected and treated are less likely to develop neurological problems or have seizures and mental retardation, though such clinical disorders are still possible. If PKU is diagnosed early enough, an affected newborn can grow up with normal brain development, but only by managing and controlling Phe levels through diet, or a combination of diet and medication. Optimal health ranges (or "target ranges") are between 120 and 360  $\mu\text{mol/L}$ , and aimed to be achieved during at least the first 10 years ( **Behrman et al., 2006**).

### **Aim**

To identify clinical profile and impacts of PKU on children, this may allow, help, and promote local

community to establish PKU screening practice for early diagnosis and treatment.

## **2. Patients and Methods**

### **Patients**

#### **Study Design:**

Observational Cohort Study.

#### **Place of study:**

Pediatric Department and Pediatric Neurology Clinic at Sohag University hospital, Upper Egypt.

#### **Period of study:**

January 2009-through June 2012.

#### **Protocol of the study:**

All infants and children with clinical suspicious of having PKU during the study period were included. The diagnosis of PKU was established based on clinical manifestations and laboratory confirmation by measuring phenylalanine level in blood sample. A verbal consent was taken from the family to conduct this research.

### **Methods**

All studied patients were subjected to thorough clinical history, full clinical examination (general, systematic, and detailed neurological examinations), and developmental assessment. Computed tomography brain (CT), Electroencephalography (EEG) was done for all patients. Phoniatric and Audiologic Evaluation were conducted for the patients.

#### **Present history:**

Detailed history of the presenting symptoms which include seizures (types, onset, progression, loss of consciousness, duration, frequency), developmental history including the main domains as gross motor, fine motor, language and social development, Autistic symptoms (as delayed language development, lack of eye contact, stereotyped and repetitive use of language...etc), hyperactivity symptoms (as often runs about or climbs excessively, often fidgets with hands or feet or squirms in seat, often talks excessively...etc).

#### **Family history:**

History of similar condition in other family members, presence of epilepsy, mental retardation or global developmental delay.

### **Clinical evaluation**

#### **General examination:**

For the presence of any dysmorphic features or features of metabolic disorders, measurement of head circumference.

#### **Systemic examination:**

For presence of features of PKU as fair hair, skin and musty odor.

#### **Neurological examination which include:**

Mental state (consciousness, behavior, intelligence), speech, cranial nerves, motor systems examination & reflexes and sensory system examination.

#### **Neurodevelopmental Assessment:**

Which include detailed neurological examinations and Denver Developmental Screening Test (DDST II) for rapid assessment of the four different components of development: personal-social, fine motor, adaptive language, and gross motor development. Stanford Binet 4<sup>th</sup> edition was performed for older children.

All patients were referred to Phoniatic Unit and were subjected to Ear, Nose, and Throat (ENT) examination.

Language evaluation (eye contact, response to examiner, eye head coordination), assessment to passive and active vocabulary.

Childhood Autism Rating Scale (CARS) and the degree of autistic disorders were done as 30 serving as a cut off for a diagnosis of autism, mild-moderate autism (30-37) and severe autism (>37)(Eric et al., 1988).

Psychometric evaluation, using Vineland adaptive Behavior Scales (Sparrow et al., 2004) & Stanford-Binet Intelligence Scales(Terman et al., 1960).

Children in this work were subjected to the following investigations:

Computed tomography (CT) scanning for the brain.

Electroencephalography (EEG).

Complete audiological evaluation was done in Audiologic Unit

**3. Results**

The cornerstone for diagnosis of our cases was measuring blood phenylalanine level. The mean phenylalanine level in the studied cases was 15.80±8.84 mg/dl, range (3.8-28.1). The total number of patients confirmed to have pheylketonuria(PKU) was twenty four cases, fifteen of them(62.5 %) boys and 37.5 % girls .The age of presentation range from 1 month to 132 months with mean age of presentation was 40.5 ± 36.04 months while the median age was 33.5 months.

Clinical features of the studied cases showed that the majority 16 of 24 cases (66.7%) have global developmental delay (affection of more than 2 developmental domains; motor, language, and social

development). While 11 cases have hyperactive symptoms. Seizures were reported in 9 cases and included four cases with generalized tonic-clonic seizures, three cases with infantile spasms, , and two cases with febrile seizures, 8 cases have autistic features according to the American Psychiatric association diagnostic criteria for autism(Arlington, 2000), Isolated language delay without autistic features was found in two cases, moderate hearing loss reported in two cases, microcephaly in 3 cases, while one case has delayed motor milestones, and one case has dysmorphic features. The studied series included 2 sisters. See table (1), figure (1).

Computed tomography (CT) of the brain showed that 14 cases (58.3%) have brain atrophic changes, 7 cases (29.2 %) have normal imaging, 2 cases have white matter disease with brain atrophy while one case have brain atrophy with lissencephaly (Table 2).Electroencephalography (EEG) was done in all cases and showed that10 cases (42.7%) have normal EEG finding, 6 cases have generalized epileptic discharges, 5 cases have focal epileptic discharges, and 3 cases have hipparrhythmia pattern. See table (3).

Table (1): Clinical features of the included cases

Clinical features	Numbers of cases	Percentages from total number (24)
Global developmental delay	16	66.7 %
Hyperactivity symptoms	11	45.8 %
seizures	9	37.5 %
Autistic features	8	33.3 %
Microcephaly	3	12.5 %
Isolated delayed language development	2	8.3 %
Hearing impairment	2	8.3 %
Dealyed motor development	1	4.2%
Dysmorphic facial features	1	4.2 %

(It is to be noted that one case may have more than one presentation)

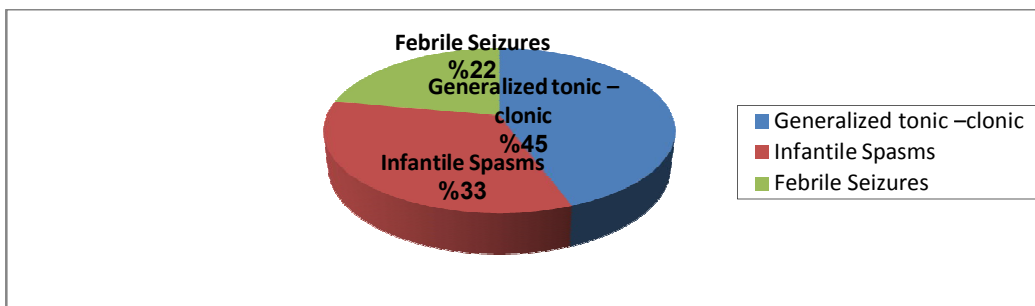


Figure (1): types of seizures reported in the studied patients

Table (2): CT Brain finding of the included cases

CT findings	Number of cases	Percentages
Normal findings	7	29.17
Abnormal Findings	17	70.83
Brain atrophic changes	14	82.35
White matter disease with brain atrophy	2	11.76
Brain atrophy with lissencephaly	1	5.88



Photo (2): 5.5 years old girl with global developmental delay, blond features.

Table (3) EEG finding of the included cases

EEG findings	Number of cases	Percentages
Normal	10	41.7 %
Abnormal	14	58.3 %
Generalized epileptic discharge	6	42.86 %
Focal epileptic discharge	5	35.71 %
Hipsarrhythmia	3	21.43



Photo (3): 11 years old boy presented by DLD in addition to other autistic features. He has blond features

List Of Photos



Photo (1): 5.5 months old girl presented by hypotonia, motor delay, blond features, microcephaly.

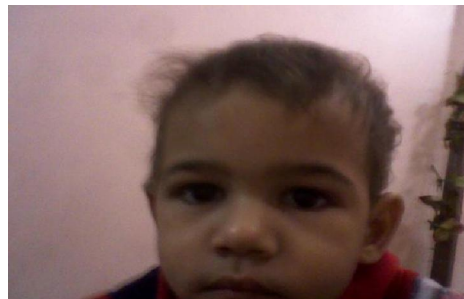
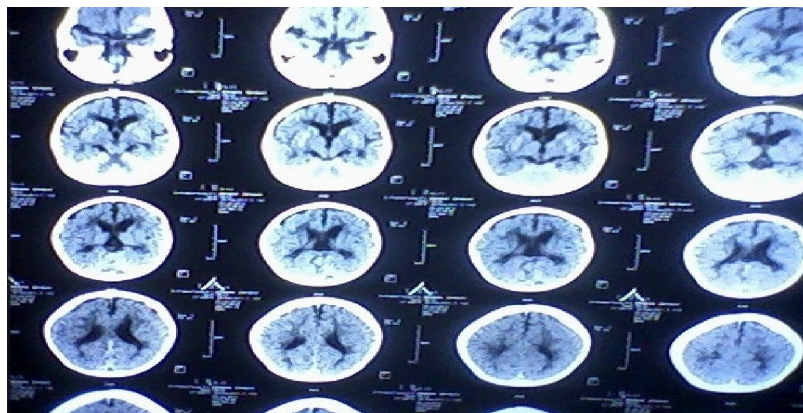


Photo (4): 18 months old boy with global developmental delay, hyperactive, blond features.



Photo(5): C T brain findings of the previous boy showing diffuse brain atrophy.

#### 4. Discussion

Phenylketonuria (PKU) is an inborn error of metabolism caused by mutation of the phenylalanine hydroxylase (PAH) gene, which reduces the rate of conversion of phenylalanine to tyrosine (*Waisbren et al., 2007*). PKU is characterized by elevated blood phenylalanine levels, which are toxic for the brain. The persistently high blood phenylalanine levels characteristic of untreated PKU are associated with mental retardation or delayed cognitive development, growth abnormalities, and behavioral difficulties, among other adverse clinical sequelae (*Paine, 1957 and Mazur et al., 2010*).

In our study we prospectively diagnosed twenty four cases with phenylketonuria with boys more common than girls (62.5 % versus 37.5%). The mean age of the studied patients was 40.5 months and this correlate with the study done in Tunisia by *Khemir et al., 2011* to evaluate the role of phenylketonuria in mental retardation they found that, the PKU estimated frequency was 1/7631 with mean age of 4 years. Our results showed that the mean phenylalanine level was 15.8 mg/dl while in Tunisia, the phenylalaninemia mean was 28 mg/dl (1680  $\mu\text{mol/L}$ ) (*Khemir et al., 2011*). our results regarding mean age were lower than that done by *Karimzadeh et al., 2012*, they evaluated 105 patients (50 boys, 55 girls) with the diagnosis of PKU. The mean age of the patients was  $8.5 \pm 6.2$  years (*Karimzadeh et al., 2012*).

In our series, the dominant clinical manifestations were global developmental delay, hyperactivity symptoms, autistic features, and seizures and this accord with the Tunisian study where they found that the classical PKU form accounted for 85.3% of cases and the dominant clinical symptoms were: mental retardation (88.2%), motor delays (87.7%), speech difficulties (83.2%) and pigmentation anomalies (61.7%). The treated patients responded to treatment and showed a normal development (*Khemir et al., 2011*).

We found that 9 cases (37.5%) had seizures; the commonest seizures types were generalized tonic-clonic followed by infantile spasms and febrile seizures. In the study done by *Karimzadeh et al., 2012*, 52.3% (55 patients) had seizure (more than 6 months before the study) and 47.7% (50 patients) were clinically seizure-free (*Karimzadeh et al., 2012*).

We found that Abnormal EEG was more common as detected in 14 cases ( 52.4 % ). Of these, generalized epileptic discharges were the commonest. While 47.6 % had normal EEG. These findings agree with the study done by *Karimzadeh et al.,* as they divided patients with PKU into case group consisted of 70 patients (66.6%) with an abnormal EEG and the controls were 35 patients (33.4%) with a normal

EEG. In the case group, 37 patients (52.8%) had a mild abnormal EEG, 10 patients (14.2%) had moderate abnormal EEG and 23 patients (32.8%) had severe abnormality in their EEG (*Karimzadeh et al., 2012*). According to Gross et al. review, in EEG recording of PKU patients, about 45% of the patients had an abnormal EEG and nearly 30% had a normal EEG in the beginning which became abnormal later (*Gross et al., 1981*). Abdel-Salam et al. study showed that 25% of the patients had seizure, but more than 50% had an abnormal electroencephalogram, which means some PKU patients had an abnormal EEG without any clinical seizure (*Abdel-Salam et al., 2005*). In *Karimzadeh et al.,* study, 44% (28 patients) of the patients with abnormal EEGs (out of 63 patients in the case group) had no clinical seizure. There is evidence that subclinical discharges can cause psychocognitive impairment and behavioral disturbance (*Karimzadeh et al., 2012*). *Karimzadeh and Tabarestani* reviewing study reported negative effects of this epileptic form discharge on the choice reaction time, verbal and nonverbal communication and behavioral disorder (*Karimzadeh and Tabarestani, 2010*).

Behavioural abnormalities were also studied in our series as they represented significant clinical presentations of PKU. Hyperactivity manifestations were the commonest (45.8%) while autistic features were defined in (33.3 %). In the study of *Karimzadeh et al.,* the behavioral-emotional scale evaluation showed the frequency of attention deficit was 85.7% in the case group and 40% in the controls. Hyperactivity was detected in 71.4% and 28.5% of the cases and controls, respectively. 85.7% of the cases showed attention deficit hyperactivity disorders in comparison with 40% in the controls. Autistic behavior was detected in 57.1% of the cases and 28.5% of the controls. Totally, the frequency of behavioral disorder was 85.7% in cases and 42.8% in control patients (*Karimzadeh et al., 2012*).

*DeRoche and Welsh, 2008* reported that despite many neuropsychological studies in treated PKU it remains difficult to draw clear conclusions: the numbers studied are often small; the types of neuropsychological test vary between studies; the ages are different (children or adults); the background phe control and phe level at the time of testing vary. The tentative conclusion is that some neuropsychological damage occurs even in treated PKU. Reaction times are delayed in PKU and this relates to concurrent elevated phe levels. Executive function i.e. higher level processes requiring interactions between several areas of the brain, has been extensively studied as it is governed by the pre-frontal cortex. This is a dopamine sensitive area of the brain which may be especially vulnerable in

PKU. Of the various subsets of executive function studies, inhibitory control is impaired in early-treated PKU. Tests of working memory may have an age-related effect as children show largely normal results but a decline in function is observed in adolescents and adults. There are other behavioural and psychiatric symptoms attributed to PKU. Poor dietary control early in life results in anxiety, hyperactivity and social withdrawal, and those with satisfactory early treatment still appear to have a higher risk of low self-esteem and possibly depression. Further research is required in this field: the size of studies must increase and their uniformity be ensured. Longitudinal projects should also be developed (DeRoche and Welsh, 2008)

In our study Computed tomography (CT) of the brain showed that only less than one third of cases have normal imaging while the majority (17 cases) have abnormal findings, brain atrophic changes and white matter disorders are the significant findings (See results). An early case PKU series published by Thompson and colleagues (Thompson *et al.*, 1990) described a pattern of periventricular white matter abnormalities seen in all six patients imaged with T2-weighted MRI. These signal abnormalities were seen to intensify with clinical deterioration in one patient with serial scans, and subsequently improved with resumption of dietary Phe restriction. A subsequent study imaged 74 PKU patients with the aim of investigating correlations between dietary Phe control and MRI signal abnormalities. The authors found that white matter signal abnormalities were present in all but one patient, and that in addition to diffusely increased signal in the posterior and anterior periventricular regions, 16 patients exhibited discrete punctate lesions within the parenchymal white matter. Additionally, the severity of signal abnormalities was higher in older patients off of dietary restriction than in younger patients still on diet, and a significant positive correlation existed between Phe levels at the time of scanning and signal abnormalities on T2-weighted MRI. Elevated T2 signal is believed to reflect intramyelinic edema in PKU patients resulting from the osmotic pressure exerted in increase cerebral Phe levels (Cleary *et al.*, 1994).

Anderson and Leuzzi, 2010; stated that brain MRI in children and adults commonly show abnormalities in the cerebral white matter even in treated PKU. These signal changes are likely to be intramyelinic oedema which usually affects the periventricular white matter. Milder changes affect only the occipital lobe but more severe involvement progresses rostrally to the frontal lobe. The degree of white matter change is associated with recent metabolic control (average phe level in the preceding

year and current phe levels) but not to early phe levels. Despite years of investigation the functional consequences of these findings are unclear. There is some recent evidence suggesting a correlation between neuropsychological performance and more widespread white matter changes. The MRI changes are reversible upon lowering blood phe within about 2 months. The lesions appear static at least over a 5-year period in adulthood if phe levels remain stable (Anderson and Leuzzi, 2010).

**Conclusion:** We can conclude that PKU still has adverse effects on children in Upper Egypt and lack of national screening programs leading to developmental problems, mental retardation, and behavioral abnormalities in these children.

### Recommendations;

We recommend establishment of national screening programs and pushing it forward, immediate development of specific metabolic centers in various universities and research institutes especially in Upper Egypt.

### Corresponding author

**Ahmed M. Emam**

Phoniatric Unit, ENT Department, Sohag University, Egypt.

[ahmedaboud2002@yahoo.com](mailto:ahmedaboud2002@yahoo.com)

### References

- (1) Anderson P J, Leuzzi V. (2010). White matter pathology in phenylketonuria *Mol Genet Metab*, 99 (Suppl 1), pp. S3–S9.
- (2) Arlington VA, American Psychiatric Association (2000): American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision (DSM-IV-TR, 2000).
- (3) Abdel-Salam GMH, Abdel-Kader AA, Inical LE. (2005). Electroencephalographic (EEG), Neuroradiological and Molecular (PKU) patients. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*; 42(2):390–406.
- (4) Behrman, Richard E.; Kliegman, Robert; Nelson, Waldo E.; Karen Marcadante; Jenson, Hal B. et al (2006). in Chapter 55, page 255 in *Nelson essentials of pediatrics*.
- (5) Cleary MA, Walter JH, Wraith JE, *et al.* (1994). Magnetic resonance imaging of the brain in phenylketonuria *Lancet*, 344, pp. 87–90
- (6) Cleary MA, Walter JH, Wraith JE, *et al.* (1995). Magnetic resonance imaging in phenylketonuria: reversal of cerebral white matter changes. *J Pediatr*; 127:251-255.
- (7) DiLella AG, Kwok SCM, Ledley FD, Marvit J, Woo SLC. (1986). "Molecular structure and

- polymorphic map of the human phenylalanine hydroxylase gene". *Biochemistry* 25 (4): 743–749.
- (8) DeRoche K, Welsh M.(2008).Twenty-five years of research on neurocognitive outcomes in early-treated phenylketonuria: intelligence and executive function *Dev Neuropsychol*, 33, pp. 474–504
- (9) Eric Schopler, Rober Reichler , and Barbara Rothen (1988). *Childhood Autism Rating Scale*, Western Psychological Service.
- (10) Gross PT, Berlow S, Schuett VE, Fariello RG.(1981). EEG in phenylketonuria. Attempt to establish clinical importance of EEG changes. *Archives of Neurology*; 38(2):122–126.
- (11) Guldberg P, Henriksen KF, Sipila I, Guttler F, de la Chapelle A. (1995). "Phenylketonuria in a low incidence population: molecular characterization of mutations in Finland". *J. Med. Genet* 32 (12): 976–978.
- (12) Gonzalez, Jason; Willis, Monte S. (Feb. 2010). "Ivar Asbjorn Folling Discovered Phenylketonuria (PKU)". *Lab medicine* 41 (2): 118–119.
- (13) James, William D.; Berger, Timothy G. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. ISBN 0-7216-2921-0.
- (14) Karimzadeh P, Tabarestani S.(2010). Promising medical treatment for childhood psycho-cognitive problems. *Neural Regeneration Research*.;5(21):1663–1667.
- (15) Loeber J G (2007): Neonatal screening in Europe; the situation in 2004 *J Inherit Metab Dis*, 30, pp. 430–438
- (16) Mayo Clinic Staff (2007-12-20). "Phenylketonuria (PKU)". Mayo Clinic.
- (17) MacLeod MD, Monroe JF, Ledingham JG, *et al.* (1983).Management of the extrapyramidal manifestations of phenylketonuria with L-dopa. *Arch Dis Child*; 58:457-458.
- (18) Mazur A, Jarołowicz S, Sykut-Cegielska J, Gradowska W, Kwolek A,Ołtarzewski M.(2010). Evaluation of somatic development in adult patients with previously undiagnosed and/or untreated phenylketonuria. *Med Princ Pract*; 19(1):46–50.
- (19) Ozalp I, Coşkun T, Tokatlı A, Kalkanoglu H .S, Dursun A, Tokol S., *et al.* (2001). Newborn PKU screening in Turkey: at the present and organization for future *Turk J Pediatr*, 43, pp. 97–101.
- (20) Paine RS.(1957). The variability in manifestations of untreated patients with phenylketonuria (phenylpyruvic aciduria). *Pediatrics*. ; 20(2):290–302).
- (21) Partington MW.(1961). The early symptoms of phenylketonuria. *Pediatrics*; 27:465-473.)
- (22) Pearsen KD, Gean-Marton AD, Levy HL, *et al.* (1990). Phenylketonuria: MR imaging of the brain with clinical correlation. *Radiology*; 177:437-440.
- (23) Parvaneh Karimzadeh , Mohammad Reza Alaei, and Hadi Zarafshan (2012).The Association between EEG Abnormality and Behavioral Disorder: Developmental Delay in Phenylketonuria, *ISRN Pediatr.*; 2012: 976206.
- (24) Sameh Khemir, Monia El Asmi, Haifa Sanhaji, Moncef Feki, Riadh Jemma, Neji Tebib, Jean Louis Dhondt, Marie Françoise Ben Dridi, Abderraouf Mebazaa, Naziha Kaabachi(2011). Phenylketonuria is still a major cause of mental retardation in Tunisia despite the possibility of treatment. *Clinical Neurology and Neurosurgery*, Volume 113, Issue 9, November, pages 727-730.
- (25) Sarafoglou, Kyriakie; Hoffmann, Georg F.; Roth, Karl S., eds.(2008). *Pediatric Endocrinology and Inborn Errors of Metabolism*. New York: McGraw Hill Medical. p. 26.
- (26) Sparrow, S, Balla , D and Cicchetti, D.(2004). *Vineland Adaptive Behavior Scales*. Circle Pines, MN: American Guidance Service. Statistics Norway.
- (27) Thompson AG, Smith I, Brenton D *et al.* (1990). Neurological deterioration in young adults with phenylketonuria *Lancet*, 336, pp. 602–60.
- (28) Terman, Lewis Madison; Merrill , Maude A. (1960). *Stanford- Binet Intelligence Scale; Manual for the Third Revision From L-M with Revised IQ tables by Samuel R. Pinneau*. Boston (MA); Houghton Mifflin.
- (29) Waisbren S, Noel K, Fahrback K, Cella C, Frame D, Dorenbaum A, Levy H (2007). Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. *Mol Genet Metab* 92: 63-70.