Intelligent quotient of late treated phenylketonuric patients: is brain damage still preventable?

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Abstract: Over the past 30 years and since the first trial to treat phenylketonuria (PKU) by Horst Bickel and his coworkers, the dietary treatment of PKU has produced a generation of adult women with PKU who have minimal cognitive deficits and are now of child-bearing age. If PKU is detected early enough in infancy, mental retardation can be prevented by giving a diet containing a restricted amount of phenylalanine. The principle of therapy is that all newborn babies with phenylalanine concentration of 360 µmol or above are to be treated as early as possible to achieve a higher mental function in terms of intelligence quotient, blood phenylalanine levels should be maintained in the range of 120 - 360 µmol/l. Subnormal as well as high phenylalanine levels are to be avoided. In the last few years there are increasing published articles on late treated PKU patients. In these patients, the mean IQ was 57. For those treated after 2 months of age, recent studies have suggested that approx. 23% of those children have normal IQ. In our hospital most of our cases were late treated (15 patients out of 22), the age at which treatment was started ranges from 2 weeks to 9 years. It is noted that those patients who were diagnosed before 2 years of age (6 children) and were on strict phenylalanine low diet with a phenylalanine maintained less than 4mg/dl have a normal IQ (75 or above) (6 patients), one child has difficulty in speech, 2 children had border line IQ (above 70 and less than 75), two children had moderate learning difficulties (IQ above 35 and below 50), 4 children had severe learning difficulties (IQ above 20 and less than 35 of which two of them diagnosed before 2 years of age.

Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder caused by a defect in phenylalanine hydroxylase activity. Its clinical manifestation is the result of a mutation in the phenylalanine and of exposure to L-phenylalanine (1). In 1934, Folling from Norway described a group of mental retarded patients who had a strong odor and a positive diaper test, and it was called Folling disease (2). The first trial for treatment was done by Horst Bickel in 1951 (3). Since the introduction of the screening program initially by Guthrie test, phenylketonuria was no longer a cause for brain damage if treatment was initiated early in life and phenylalanine levels were maintained in normal levels (4, 5).

Dietary treatment is based on phenylalanine restriction and supplementation of essential amino acids, the concept of diet for life is increasing and cost effective (6-8); however the benefits of late treatment or diet resumption in adults is a matter of controversy (9-11).

In Libya, as well as in many developing countries, there has been no screening program yet. Most of the cases were late diagnosed and late treated. Our PKU clinic was started in 1997. First patient was diagnosed in our hospital in 1997; he presented with a developmental delay and fair hair at age of 19 months. Since that time we have diagnosed many cases.

Materials and methods

Patients: nineteen patients have been attending our clinic regularly. Seven males and 12 females, with 4 families have more than one affected child. Most of the cases were a result of a first degree consanguineous marriage. All affected children were born at full term. Mean birth weight was 3 kg. Four children were early diagnosed before two weeks of age, the rest were late diagnosed (15/19). The mean age at the time of diagnosis was 28 months, ranging from 7 months to 9 years.

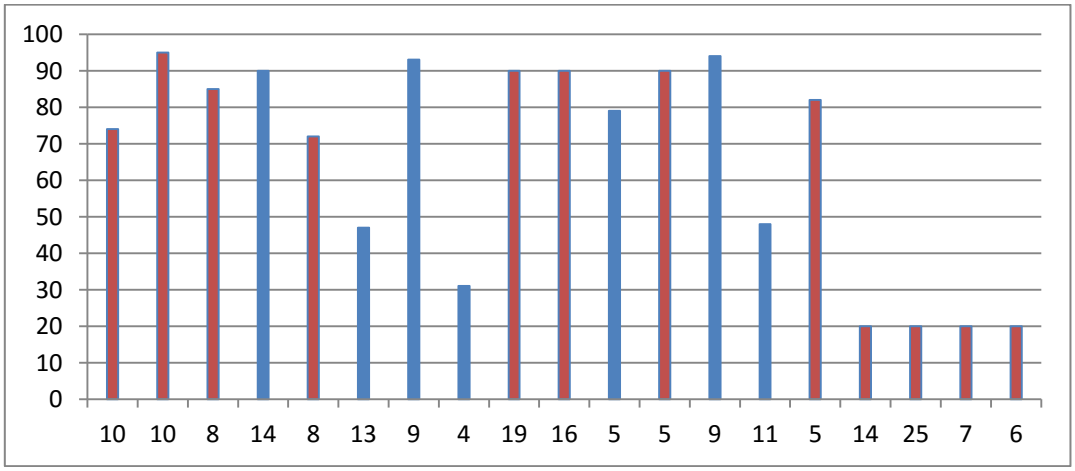
The mean phenylalanine level at time of diagnosis was 20 mg/dl = 1200 µmol/l) ranging from 600 - 2400 µmol/l. All of late treated patients presented with developmental delay, in addition to developmental delay 3 had eczema, 5 patients had also Athetotic movements in upper limbs, only one female diagnosed at 9 years had convulsion.

Developmental assessment: Developmental assessment was not done in 5 patients, one because of early treatment and now attends collage, 2 attend high school, and the other 2 children had severe developmental delay and developmental assessment could not be carried out. Griffith's developmental scales were developed by Ruth Griffiths, in 1954 and revised in 1996. Ruth Griffiths (12), the scale is the most common development scale used in UK. It is a screening test and is not valid for prediction. It concentrates on the abilities of the child. The accent is on what the child can do rather than what he cannot do. All the tests were carried by one examiner (AZ) to eliminate errors due to differences in interpretation. Parents of the child were present throughout the testing whenever this was possible. All the information was entered on the form at the time of the test. All ages were worked out as a routine with a calendar. All the process of counting, addition and works on chart were carried out at least twice.

Results

In Table 1, 2 patients were early diagnosed had GIQ ≥ 79. 15 children out of total of 19 who have been attending our clinic were late treated patients. Four patients out of the 15 (34%) are severely mentally handicapped of whom 2 diagnosed before 24 months of age. One patient who is 32 months old has delayed speech and language. Six children (40%) had IQ ≥ 90, of whom one has neurofibromatosis with myopia. Two females (14%) had moderate learning disability, their IQ 47, 48. Two patients (14%) had border line IQ of 74, 72. It is observed that 7 children had delay in performance against time, although they have normal or border line IQ and 4 patients have both delay in performance and practical reasoning.

Table1: Age in years, sex and IQ



Discussion

Fifteen of the patients were diagnosed before 2 years of age except for two patients (2 sisters) who are severely mentally handicapped and they were not on strict phenylalanine diet, they are diagnosed as atypical PKU (DHPR deficiency). In two patients who were too late diagnosed at 7 and 9 years (brother & sister), there were an improvements in IQ of the brother who is moderately mentally handicapped and cessation of fits in the sister who became calmer and quite (15-17). We have observed that most of late treated patients have delay in performance against time.

Intelligence quotient was significantly higher in patients, who continued on phenylalanine restricted diet (13), diagnosed between seven months and nine years, mean age 28 months, It is considered that the age of diagnosis is very late compared to published studies (13-17). 40% of our children had an IQ above 90, this is higher than Leuzzi study which showed that 23% of late treated patients had a normal IQ (16), 14% of our patients had moderate learning disabilities (IQ 47, 48), 14% had border line learning disabilities (IQ 72, 74) and 34% were severely mentally handicapped. This figure is almost similar to that reported by Koch R (32% were severely mentally handicapped), although the age of diagnosis and treatment were earlier than in our patients (3 months) (14-18). Our patients who have a normal IQ are those who were diagnosed before 2 years of age (12 patients), 3 of them were diagnosed less than one month of age, these patients were on strict diet and their phenylalanine levels were less than 4 mg/dl. Our recommendation: late diagnosed PKU patients should be started on low phenylalanine diet with monthly monitoring of phe levels which should be between 2 - 4 mg/dl.

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There is no competing interest and ethics is approved by Hospital's scientific committee.

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