RESEARCH PAPER

Factors Influencing Verbal Intelligence and Spoken Language in Children with Phenylketonuria

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Objectives: To determine verbal intelligence and spoken language of children with phenylketonuria and to study the effect of age at diagnosis and phenylalanine plasma level on these abilities.

Design: Cross-sectional.

Setting: Children with phenylketonuria were recruited from pediatric hospitals in 2012. Normal control subjects were recruited from kindergartens in Tehran.

Participants: 30 phenylketonuria and 42 control subjects aged 4-6.5 years. Skills were compared between 3 phenylketonuria groups categorized by age at diagnosis/treatment, and between the phenylketonuria and control groups.

Main outcome measures: Scores on Wechsler Preschool and Primary Scale of Intelligence for verbal and total intelligence, and Test of Language Development-Primary, third edition for spoken language, listening, speaking, semantics, syntax, and organization.

Results: The performance of control subjects was significantly better than that of early-treated subjects for all composite quotients from Test of Language Development and verbal intelligence (P <0.001). Early-treated subjects scored significantly higher than the two groups of late-treated subjects for spoken language (P =0.01), speaking (P =0.04), syntax (P =0.02), and verbal intelligence (P =0.019). There was a negative correlation between phenylalanine level and verbal intelligence (r= –0.79) in early-treated subjects and between phenylalanine level and spoken language (r= –0.71), organization (r= –0.82) and semantics (r= –0.82) for late-treated subjects diagnosed before the age one year.

Conclusion: The study confirmed that diagnosis of newborns and control of blood phenylalanine concentration improves verbal intelligence and spoken language scores in phenylketonuria subjects.

Keywords: *Development, Management, Outcome, Pheylalanine*.

The prevalence of phenylketonuria (PKU) is high in Iran [1,2]. Elevated levels of phenylalanine (Phe) in plasma cause mental retardation, seizures, behavioral problems, and delay in motor and language development [3,4]. Although early-treated children with PKU have been found to be of average intelligence, they have shown differences in cognitive function with normally developing peers [5-7]. The academic and cognitive functions of children with PKU are significantly lower than age–matched controls [8,9].

Some investigations have reported conflicting results for language development in early-treated PKU children [10-13]. Although language problems have been reported [10], some studies do not confirm language delay in children with PKU [11,12]. A relationship between cognitive function, verbal ability and blood Phenylalanine level has been demonstrated [6,11,14]. Early and consistent dietary therapy for PKU has been shown to increase the IQ of afflicted children [15-17].

The present study investigated the effect of age at diagnosis, treatment onset, and Phenylalanine concentration on language development.

Methods

In this cross-sectional study, children diagnosed with PKU aged 4-6.5 years were recruited from three pediatric hospitals in Tehran. All enrolled patients had been assessed for one year (2012-13). It was observed during assessment that the late-treated group was heterogeneous. In order to produce more homogenous groups, the children were placed into one of three groups based on age at diagnosis: early-treated PKU subjects (diagnosed by newborn screening), late-treated PKU subjects (diagnosed before the age of one year) and late-treated PKU subjects (diagnosed after age one). The age at diagnosis, treatment onset and blood Phe level were taken from patient clinical records

Inclusion criteria for subjects were blood Phe higher than 6 mg% in the first stage of diagnosis [18], treatment

only by control of Phenylalanine, normal hearing, Intelligence Quotient (IQ) above 50, native speaker of Farsi, and able to undergo verbal testing (nonverbal patients were excluded). The average blood Phe levels were calculated for the six months prior to onset of the study. A level of Phe ≤6 mg% indicated strict dietary control of PKU [18].

An audiologist assessed hearing by Otoacoustic emissions (OtoRead Handheld OAE device; Interacoustics). Pure tone audiometric screening was carried out bilaterally for 25 dB HL ISO at 500, 1000, 2000 and 4000 Hz. A psychologist assessed verbal intelligence and total intelligence using the validated and standardized Farsi version of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) [19]. WPPSI subtests used for assessment of verbal intelligence were information, vocabulary, arithmetic, comprehension, and similarities. A speech therapist assessed language skills of subjects using the validated and standardized Farsi version of the Test of Language Development-Primary, third edition (TOLD-P: 3) [20]. The main TOLD-P: 3 subtests used were: Picture vocabulary: evaluates understanding of the meaning of spoken words; Relational vocabulary: evaluates understanding of the relationship between two spoken words and ability to explain the relationship orally; Oral vocabulary: evaluates the skill in relating oral meanings of words spoken by the examiner; Syntactic understanding: evaluates the skill to understand the meaning of sentences; Sentence imitation: evaluates the skill to reproduce sentences spoken by the examiner; and Morphological completion: evaluates the skill to recognize, comprehend, and use usual morphological forms.

Several subtests were combined to develop composite scores for semantics, syntax, listening, organizing, speaking, and spoken language. The Farsi version of TOLD-P: 3 utilizes standard scores with a mean of 100 and SD of 15 for composites and a mean of 10 and SD of 3 for its subtests.

Children with apparently normal development were selected as control group randomly from kindergartens in Tehran and were matched with the PKU subjects for age, gender, and level of mother's education. Their hearing and IQ were tested to be in normal ranges and they were native speakers of Farsi.

All procedures were in accordance with the ethical standards of the Committee for Ethical Study of Human Subjects at Tehran University of Medical Sciences and with the Helsinki Declaration. The purpose of the study was explained to the parents of the subjects. The parents of all PKU and control subjects signed written informed consent forms before participation in the study.

Statistical analysis: The normal distribution of data was assessed using the Kolmogorov-Smirnov test. One way ANOVA and Tukey honestly significant difference (HSD) test in post-hoc multiple comparisons were used to compare the composite quotients from TOLD-P:3 and verbal IQ independently for the PKU and control groups. The Spearmen correlation used to detect relationships between mean blood Phe levels and composite quotients of TOLD-P: 3 and verbal IQ and to find the relationship between the spoken language quotient with total IQ and verbal IQ ($P<0.05$).

RESULTS

A total of 42 PKU patients were assessed for the study, and a similar number of controls were selected. Twelve PKU patients were excluded. Their age at diagnosis was between 8 to 24 months. One had hearing loss, 1 was diagnosed with autism, and 10 were severely intellectually disabled and nonverbal. The 30 PKU subjects included 13 late-treated subjects diagnosed before age one, 9 late-treated diagnosed after age one, and 8 early-treated. The mean (SD) age of early treated, late treated <1 year age, later treated ≥1 year age and control groups was 51.1 (8.04), 58.3 (8.87), 68.8 (9.25) and 59.6 (10.81), respectively. Phe levels ≤6 mg were seen in 50%, 41.7% and 46.2% of the three study group, respectively. Treatment for all PKU subjects had begun when the disorder was diagnosed. The lowest age at diagnosis was newborn and the highest was 26 months. All late-treated children but none of the early-treated subjects had received rehabilitation. The mean Phe level in the subjects in the treatment groups was 2.50 to 14.5 mg%.

***Table* I** shows the trend of mean for verbal and total IQ and all composite quotients. There were significant differences between all PKU groups and the control group for verbal and total IQ and all composite quotients ($P<0.001$). The mean of spoken language ($P=0.01$), speaking ($P=0.04$), and syntax ($P=0.02$) were significantly higher in early-treated subjects compared to late-treated subjects diagnosed before age one year. The mean of all composite quotients were significantly higher in early-treated subjects compared to late-treated subjects diagnosed after age one year ($P\leq0.002$). A significant difference was observed between the two groups of late-treated subjects for all composite quotients ($P\leq0.04$), except organizing.

The results of Phe level versus composite quotients for TOLD-P: 3 showed significant negative correlations

TABLE I MEAN (SD) RESULTS OF INTELLIGENCE AND LANGUAGE TESTING OF STUDY POPULATION

Variables	*Control*	*Early-treated*	**Late-treated (<1y)*	**Late-treated(>1y)*
Spoken Language	99.55(6.35)	83.37(8.53)	70.44(14.13)	56(8.65)
Listening	98.55(7.07)	86.62(9.15)	78.33(10.98)	65.78(7.61)
Speaking	98.95(6.84)	84.62(5.26)	74(11.64)	64.7(9.95)
Semantics	100.95(6.5)	88.37(7.69)	78.78(14.74)	98.85(9.98)
Organizing	99.69(8.63)	82.37(11.1)	70.67(14.42)	64.92(11.3)
Syntax	97.26(7.59)	80.25(10.09)	68.11(10.94)	57.68(8.68)
Verbal IQ	108.67(9.1)	92.12(13.79)	77.22(13.29)	64.92(8.94)
Total IQ	108.24(99.45)	88.78(12.37)	72.33(14.41)	60.69(7.85)

Values are expressed as Mean (SD), P <0.001; IQ by Wechsler Preschool and primary scale of intelligence and Language testing by Test of Language Development, 3rd edition.

**Late treated subjects diagnosed before or after 1 year of age.*

between Phe level and the spoken language, organizing and semantics quotients for late-treated PKU subjects diagnosed before age one year. There was no significant correlation between Phe level and composite quotients in early-treated PKU subjects and late-treated PKU subjects diagnosed after age one. The relation between verbal IQ and blood Phe level showed a significant negative correlation in early-treated PKU subjects. This correlation was not observed for the late-treated PKU groups (***Table* II**).

There were significant correlations between total IQ and spoken language quotient for the control group (r= 0.54, P<0.001) and late-treated PKU groups (r = 0.68, P<0.001). There was no significant correlation for the early-treated PKU group (r = 0.29, P=0.49).

A significant correlation was observed between verbal IQ and spoken language quotient for the control group (P<0.001) and late-treated PKU groups (P= 0.02). There was no significant correlation for the early-treated PKU group (P= 0.38).

DISCUSSION

We found verbal IQ for all PKU groups to differ from that of the control group. The composite quotients for TOLD-P:3 showed that the performance of the early-treated group was lower than average, the late-treated group diagnosed before age one performed poorly, and late-treated group diagnosed after age one performed very poorly for language skills. This study did not show a consistent relationship between Phe level and language performance using TOLD-P:3 and verbal IQ.

The present study had some limitations. The first was that there has been little study of language abilities in children treated late for PKU, because most countries now test for the condition in newborns. This means that it is was not possible to compare the results of the present study with those of previous studies to assess language impairment in late-treated PKU subjects. The second limitation was not being able to test for serum Phe concentration on the day of assessment. The most recent assessment time was up to six months prior to onset of the

TABLE II RELATION BETWEEN PHENYLALANINE LEVEL AND LANGUAGE ABILITY IN CHILDREN WITH PHENYLKETONURIA

	Mean blood Phe level		
Variables	*Early-treated (n=8)*	**Late-treated (<1y) (n=9)*	**Late-treated (>1y) (n=13)*
Spoken language	-0.143 (0.736)	-0.711(0.032)$^{\$}$	0.144 (0.640)
Listening	0.122 (0.774)	-0.531(0.141)	0.537(0.059)
Speaking	-0.209 (0.620)	-0.636 (0.066)	-0.014 (0.963)
Semantics	0.193 (0.647)	-0.817 (0.007)$^{\#}$	0.151(0.623)
Organizing	-0.301 (0.468)	-0.814 (0.008)$^{\#}$	-0.252 (0.406)
Syntax	-0.216 (0.608)	-0.636 (0.066)	-0.144 (0.640)
Verbal IQ	-0.786 (0.021)$^{\#}$	-0.269 (0.484)	-0.024 (0.938)

*$^{\$}$P<0.05, $^{\#}$P<0.01; *Late treated subjects diagnosed before or after 1 year of age.*

What is Already Known?

- Impaired language skills occur in children with Phenylketonuria.

What This Study Adds?

- Early-treated and late-treated subjects with PKU experience language impairment, but impairment is more severe in late-treated subjects.

study to calculate mean blood Phe level.

The present results support the findings of previous researchers [5,6,9] who reported that early diagnosis and intervention prevents mental retardation. The spoken language results demonstrated that this metabolic disorder affected language even in subjects who were diagnosed early. These results conflict with the findings of Melnick, *et al*. [10], Michel, *et al*. [11] and Ozanne, *et al*. [21]. They found no pattern of linguistic deficit in early-treated subjects. Zartler and Sassaman [12] found that language skills in early-treated children were in the average range. The source of the disagreement with the findings of the present study apparently stems for the different aspects of language that were assessed. We found that subjects with PKU were more vulnerable to problems with organizing than for other language skills. This may have been related to the type of the tasks that were used for assessment. These tasks involved memory and semantic clustering, which are related to executive functioning [22]. These results must be interpreted with some caution because the executive function was not measured as extensively as in other studies [23,24]; however, it appears that children with PKU experience difficulty with executive functioning.

The findings on total IQ in late-treated children agreed with the findings of other researchers [3,14]; however, no study was found that investigated language skills in such children. A clear deficiency in intelligence and language from early stages of development is illustrated by the findings of the late-treated subjects for the relationship between verbal IQ and the spoken language quotient. The reason that most previous studies did not find significant differences between normally developing and early-treated PKU subjects probably stems from the usage of verbal IQ as a scale for language assessment.

The results correspond to those of previous studies [11,14] that increased blood Phe levels decreased verbal IQ in early-treated children. Ozanne, *et al*. [21] did not report a consistent relationship between language skills, cognitive abilities, or dietary control ratings in early-treated children. The relationship between Phe level and organizing, spoken language ability, and semantics in late-treated subjects diagnosed before age one year suggests that these skills can improve with strict control of Phe level. This result confirms that strict dietary control is necessary for late-treated children.

The results of the present study suggest that authorities in developing countries must be diligent in carrying out newborn screening and education of families with children afflicted with PKU about dietary control. More research focused on language assessment is needed to better understand the mechanism of language impairment, to investigate causality and for continued longitudinal follow-up.

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