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Investigation of Main Risk Parameters for Mental Retardation Development in PKU Patients in Armenia

A THESIS Project

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ABSTRACT

This study was focused on problems in the management of PKU patients related to health outcomes in Armenia. PKU (phenylketonuria) is a genetic disorder, which causes mental and

physical retardation in untreated children. PKU as a disease can not be prevented if the child has a genetic predisposition. But severe mental retardation as a consequence can be prevented if the disease is diagnosed early and appropriate dietary treatment is met. However, the majority of patients with PKU in Armenia have severe mental retardation. Routine screening, a standard practice in many countries, is not done for new-borns in Armenia now. Phenyfree formula although available was received by minority of PKU patients. There are children with different health outcome even among PKU patients. The majority have severe mental retardation.

The objectives of this study were to assess the health care management of diagnosed PKU patients in Armenia and to investigate risk factors that effect the health status of Armenian PKU patients.
A case series study was conducted and evaluative judgment was based on data from this cases. 29 PKU patients from 0 to 16 years for whom PKU was diagnosed using blood test were included in the study

As any case series study requires the definite hypotheses were stated, then variables which can be potential risk factors for development of complications in PKU children were derived, data collection form has been developed in a way that data can be collected about this factors for each patient, the data were collected using several data sources, data analyses was performed in order to reveal the relationships of this factors to child's health outcome as a dependent variable.

This study observed the following risk factors that associated with health outcome of the patients: not appropriate system for diagnosis; absence of routine screening for newborns; insufficient provision of food; poor attendance of physicians office; poor control by blood screening; low knowledge of parents and lack of information for them about the disease.

INTRODUCTION

Background information about the disease

PKU (phenylketonuria) is a genetic disorder, which displays as a deficiency in the child's ability to break down the protein in food.

In healthy individuals the enzyme phenylalaninehydroxylase converses phenylalanin to the aminoacid tyrosine. In child with PKU this chemical reaction is blocked because of phenilalanynehydroxilase's defect. The consequence is high concentration of phenylalanin in blood and high phenylketon concentration in the urine. This disorder causes mental and physical retardation in the untreated children (1).

PKU is an autosomal recessive disorder. In general population one in 50 to one in 70 is PKU carrier. Approximately one child in 15,000 births is born with PKU in USA (there is a difference between ethnic groups) (1), one in 10 000 in Russia (2), higher incidence rate is in Ireland and Western Scotland - one in 5 000 birth (3).

Several clinically and biochemically distinct forms of hyperphenylalaninemia exist.(1) The main of them are:

1**. Classic PKU.** The defect in metabolism is associated with less than 2% activity of normal phenylalaninhydroxilase.

2**. Hyperphenylalaninemia due to deficiency of cofactor tetrahydrobiopterin** or malignant hyperphenilalaninemia

3. **Benign hyperphenylalaninemia**. Deficiency of phenylalanine hydroxilase ranged from 1-35% of normal.

A study was done in order to find out contemporary proportion of forms of PKU . The study showed that two-thirds of those with persistent hyperphenylalaninemia prove to have classic PKU, 1% of confirmed positive patients had regeneration of cofactor tetrahydrobiopterin, others had non-classic PKU with less intense.(4) Another study was done in Dutch. In period 1974-1989 11.000 infants were screened for PKU. 158 of them were positive for the disease. Among them classic PKU- 137 children, benign form 19, and malignant 2.(5)

The affected infant is normal at birth. The clinical manifestation of classic PKU is expressed at 3 to 6 months of age by developmental delay. Most infants have skin rash, musty odor, hyperactivity,

vomiting, widely spaced teeth. This children are blonder than unaffected siblings. One fourth of them have seizures. (6)

There are several laboratory tests which can be used to screen for PKU. Large scale newborn screening for PKU using urine was begun in California in 1957 (3). Screening of urine by FeCl was implemented routinely in USSR in 1960 -s (2). The use of the Guthrie bacterial inhibition assay for newborn screening was begun in USA in 1961-62. Now screening for PKU measuring phenylalanine in the infant's blood is well-established in USA and many other industrialized countries.(3)

Based on knowledge of the mechanism of the disease prompt treatment with Phe restricted, tyrosine supplemented diet is required for PKU patients. The objective of nutrition support is to maintain Phe concentration that will allow optimum growth and brain development. (1) Initiation and monitoring of nutrition support is described in literature. A formal prescription of the food must be written by physician-specialist. The prescription should be individualized for each patient depending on his/her specific degree of impaired ensime activity, age, growth rate, and consequent needs. Adjustment in the diet prescription is necessary based on growth, development and laboratory analysis of plasma phenylalanine concentration. During first year of life the weekly adjustment is required. Then , when the diet is altered, it can be done once every 6 month. (1)

Risk factors

PKU as a disease can not be prevented if the child has a genetic predisposition. There is a 25% probability that a child will be born with the disease when both parents are PKU carriers. But severe mental retardation and other symptoms as a consequence can be prevented if the disease was early diagnosed and appropriate dietary treatment was met (6).

Specialists give different assessment to effectiveness of treatment of classic PKU. The results of a study published by Dutch National PKU Steering committee suggests that the disease manifestation highly depends on the form of PKU at birth.(7) On the other hand there is a study which proves importance of another factors. In the course of the German Collaborative PKU Study the results of the

personality Questionnaire for children of 58 10-y-old patients treated early for PKU were analyzed. The main message of the data was "patients with PKU who were treated early and strictly did not show a higher risk for severe emotional and behavioral maladjustment compared with healthy controls at the age of 10 y".(8) Anyway, the opinion of all specialists is that early screening and early initiation of dietary treatment can improve health situation of PKU patients and prevent severe mental retardation. "PKU has become a paradigm of a disease that can be identified by screening in new-born period and treated to prevent serious complications." (9) Studies also showed effectiveness of nationwide programs regarding PKU diagnoses:" The clinical manifestation of classic PKU are rarely seen in those countries in which neonatal screening programs for the detection of PKU are in effect."(6)

Though numerous studies showed that early start of treatment is determinant of health status of PKU patient (10) (8), the reasonable concrete age when to start treatment for prevention of severe consequences varies in different sources. If not treated before 3 weeks of age the metabolic imbalance produces irreversible mental retardation, according the authors. (1) Others says that a normal development is possible if treatment is started within 3 months of life (11).

Early initiated and appropriately controlled nutrition support is crucial for prevention of serious complications in PKU patients. 25 children with early treated PKU were studied at the age of 14 years by German authors. The IQ was higher in subgroup of children with good dietary control compared to children with poor control.(8)

Another aria of concern involves the age of discontinuation of restrictive dietary therapy in children. Some early reports concluded that discontinuation of the special diet was safe after myelination of the central nervous system had been complete, by approximately age 6 or 7 (2). More recent data have documented the loss of intellectual function some years after relaxation of dietary restriction. For this reason most treatment centers in different countries now recommend that diet be kept for life. (10) (12)

Breastfeeding being worth while for PKU babes is an special issue. For many specialists it is common to think that this infants mast be fed by special formula as soon as disease is diagnosed (13). There are however studies which make this assertion doubtful. There were no significant difference between breast-fed and formula-fed infants for serum Phe, tyrosine, length, weight, head circumference. It was concluded that " Breast feeding may be continued in the newly diagnosed PKU infants without any apparent adverse nutritional consequences."(14) The same comparison was done by German authors. " No significant differences between both groups were observed for weight gain, the daily Phe intake and mean plasma phe concentration. This study shows that breast feeding can be continued in young infants with there difficult to predict weight gain and daily changing phe requirements."(15)

Caring of a PKU child requires everyday attentive control and follow-up. That is why knowledge and diligence of parents is very important for the outcome of the disease. "Misunderstanding of diet requires additional education of parents. The success of early diet management rests with the parents and depends on their understanding of the disease and their ability to cope with the diet." (1)

Current practice in Armenia.

The newborn urine screening was performed at Delivery Hospitals in Armenia and in whole USSR permanently during previous decades.

Routine screening is not done for new-borns in Armenia now. Disease is revealed only when the parents of a child refer to a medical office with complaints. Based on existing clinical display the physician sends the patient to the medico-genetic laboratory. There is only one medico-genetic laboratory in Yerevan where the test for PKU is done. Children with positive screening tests are sent to the neurogenetist's office which is in the Children Hospital #6. The office physician is responsible for consultation and the ongoing management of patients with PKU as well as with the distribution of dietary food when available.

There are 80 children at the age from 0 to 16 years on the list of PKU patients in the neurogenetist's office. Approximately 30-35 of them attend physician's office. About others no information is available since the disease was diagnosed for them. It can be supposed that health situation of this not

attending children is worse because of poor treatment and follow-up. Another point is that crude estimation of rate of the disease in Armenia shows that only one child out of 40 000 born children has the PKU which is much lower than in other countries. This can be the result of underdiagnosis. There is a special recordbook for formula distribution in the office. Every child has also his recordbook.

Special phenylfree food was available for PKU patients during last decades of Soviet Power in definite settings of distribution, though the variance of the food was limited. The situation of last years was different . Phenyfree formula was distributed to PKU patients by MOH through neurogenetist's office only intermediately and in insufficient amounts. Approximately only 30 of patients out of 80 come to receive it. The formula is not available in commercial drug-stores.

In September 1997 fenylfree formula was provided by "Aznavur fond". The amount of the formula is enough for approximately 2 years for all diagnosed PKU children in Armenia. The distribution of the food is started on September 24 and will be performed monthly.

There are children with different health outcome even among PKU patients. The majority have severe mental retardation.

OBJECTIVES

For the last tree decades PKU is known as a disease that can be identified by screening in new-born period and treated to prevent serious complications.

Taking into consideration the fact that the majority of PKU patients in Armenia have severe mental retardation and based on information about above described problems in health care management of diagnosed PKU patients in the country the following objectives of the study were defined:

- assessment of health care management of diagnosed PKU patients in Armenia
- investigation of risk factors that effect the health status of Armenian PKU patients.

METHODS

A case series study was conducted in order to meet the objectives. The investigation of series of cases was conducted and evaluative judgment was based on data from this cases.

The applied study design was considered to be appropriate in agreement with following reasons/determinants, supported by literature:

- peculiarity of the disease doesn't allow the collection of a large sample size;
- the study is aimed to make a decisions about appropriateness of health services delivery for KU patients;
- subjects of the study are patients who have the same problem and who use the same source of health care;
- the well known standards of the disease management which support normal development of the patients were used in the study as a guide.

As any case series study requires the definite hypotheses were stated, then variables which can be potential risk factors for development of complications in PKU children were derived, data collection form has been developed in a way that data can be collected about this factors for each patient, the data were collected using several data sources, data analyses was performed in order to reveal the relationships of this factors to child's health outcome as a dependent variable.

Hypotheses 1. Majority of study patients were diagnosed late, specifically later than within the first 3 months of age. Early screening was better performed in children with better health outcome.

Hypothesis 2. There is a positive association between early diagnoses and family history of PKU.

Hypothesis 3. More patients with better health outcome got early diet initiation and appropriate follow up than patients with severe forms of retardation.

Hypothesis 4. There is a positive association between availability of special phenylfree food and acceptable concentration of Phe in blood of PKU patients.

Table 1 shows variables to be measured which are derived from stated hypothesis.

Table 1. Variables/risk factors to be measured.

independent variable	measurement criteria	type of variable
1. Early diagnosis of PKU	1. Age of a child when PKU was first diagnosed. 2. Pku diagnosed within the first 3 months of life.	1. continuos 2. dichotomies
2. Baseline Phe level.	1. Level of Phe at the first screening test	1. continuos

3. Phe level control and monitoring.	1. Screening test performed during the last 6 months;	1. dichotomous
4. Dietary treatment initiation.	1. Diet initiated within 1 month after diagnosis.	1. dichotomous
5. Diet follow up, control, monitoring.	1. Availability of special phenylfree food; 2. Sources of the food; 3. Availability of a diet record. 4. Physicians attendance (visit in last 6 month).	1. dichotomous 2. categorical 3. dichotomous 4. dichotomous
6. Sours of health care provision.	1. Source of disease detection: who referred for screening 2. Source of the first screening for PKU detection; 3. The main source of medical care for PKU.	1. categorical 2. categorical 3. categorical
7. Parent's knowledge and believes.	1. Knowledge scores calculated based on right answers on questions.	1. continuous
10. Sources of information about the disease for mom.	1. Availability of information sources other than neurogenetist's office.	1. dichotomous
dependent variables		
11. Child's health outcome.	1. mental health assessed by psychiatrist trough Russian classification; 2. child's development level estimated by Harold Ireton developmental charts; 3. concentration of Phe in blood at current test.(acceptable vs not acceptable) 4. seizures in disease history; 5. school attendance.	1. categorical (ranked) 2. dichotomous 3. dichotomous 4. dichotomous 5. dichotomous

Three sources of data were used in the study.

*Data Sources***.** - Interview with the parent\guardian using the questionnaire.

- Records in physician's office.

- Record about current visit.

Data collection form includes 3 main sections: questionnaire for parent\guardian, record review part and section for registration of health status of the patient. Questionnaire contains items regarding disease diagnosis, treatment and control of the disease, availability of special food, sources of medical care and information, food intake and parents' knowledge. Record review was performed for some of questionnaire items (disease diagnoses, treatment and control, sources of medical care). In the cases when this information was available from only one of two sources (record or parent) the case was considered. In the case of some discordance between data received from two sources of information the priority was given to data from the records in order to avoid the recall bias.

The following indicators of current health status were registered in the section of health outcome:

- mental health was assessed by psychiatrist trough Russian classification which is currently used in Armenia (psychiatric test);
- for identification of child's development level two columns ("speech" and ...) of Harold Ireton developmental charts were completed by parent with the help of the pediatrician and assessed for children in age 7 years and lower;
- screening test for concentration of Phe in blood was required to perform in Medico-Genetic lab before coming for special food.
- seizures in disease history was considered one of the outcomes;
- school attendance of school age patients were assessed during the interview.

Inclusion criteria: any child from 0 to 16 years for whom PKU is diagnosed using blood test who visited Hosp #6 between September 24 and October 10.
29 patients were included in the study.

Starting from September 1997 new phenylfree food is provided monthly to all children with PKU who comes to receive it in the Hosp. #6. During this visits the questionnaire was administered by study investigator, the child was examined by the neurogenetics and psychiatrist, the Ireton chart was completed by the patient's caretaker with help of pediatrician and the child was included in the study. Further record review was performed for the same patient by study investigator.

Analyses: EpiInfo computer program was used for data analyses. Frequency of potential risk factors for development of complications in PKU children was detected and the relationships of this parameters to child's health outcome as a dependent variable was revealed using the method of univariate analyses. The same method was performed for defining the association between some risk factors.

RESULTS

The only information which is available about all children in the list of PKU patients is their year of birth and residency. There are 34 children out of 80 from Yerevan and 44 from regions, mostly close

to Yerevan. Age distribution was as follows: 8 - 16 yr. n= 45 (56 %); 3-7 yr. n=19 (24 %); 0-2 yr. n=16 (20 %).

Study population

29 PKU patients were included in the study. 26 of them were interviewed and examined by the specialist during the visits to hospital. About 3 others information was collected trough record review and phone calls.

Demographic characteristics

Residency of the study population was presented by 3 categories. Out of 29 patients 12 live in Yerevan, 14 in Armenian regions close to Yerevan and 3 out of the country (all in Russia). special food is provided are situated in Yerevan. There were 16 male and 13 female patients in the study group. The age distribution of study children was as follows: 8-16 yr. n=10 (35%); 3-7 yr. n= 12 (41%), 0-2 yr. n= 7 (24%). Such a difference in percentages of age distribution can be explained by the fact that children in younger ages need more careful medical care.

Health status characteristics

Frequencies of different outcome variables of health status were estimated and compared to each other.

Results of mental health assessment using psychiatric analysis were available for all patients and were taken as a main outcome measure for subsequent analyses. The classification distinguishes 5 categories depending on extent of severity of mental retardation. Frequency is presented in the Table 2.

Table 2. Frequency of different stages of mental retardation among PKU patients included in the study (psychiatric test results) .

Category of mental health	Freq.	Percent	Cum.
1. Normal mental development	7	24.1 %	24.1 %
2. Mild mental retardation (debility)	4	13.8 %	37.9 %
3. Moderate mental retardation (imbecility not accented)	4	13.8 %	51.7 %
4. Moderate mental retardation (imbecility accented)	11	37.9 %	89.7 %
5. Severe mental retardation	3	10.3 %	100.0 %

Total	29	100.0 %	

In addition Harold Ireton Developmental Charts were used to assess health outcome as a dependent variable. The assessment was performed for 19 patients only, because this method is applicable for children at age below 6.5 years. The categories assessed were “gross motor” and “language skills”. Children were divided into two categories based on development level. The categories were defined as follows:

1. “normal” - “ Shows behavior that is at or around age level within his\her age group. Within 30 % of actual age...” (16)

2. ‘questionable development” - “Shows development at a level which is less mature than significantly younger children- less mature than children who are 30 % younger”. (16)

Comparing the results of mental health assessment using psychiatric test with the identification of child’s development level by Harold Ireton developmental charts certain conformity was found. (see Table.3)

Table 3. *Comparison of categories assessed by psychiatric analysis and by Harold Ireton charts*.

	Gross Motor		**Language**		
Category of mental health	normal	questionable	normal	questionable	tot
1. Normal mental development	5	0	5	0	5
2. Mild mental retardation (debility)	1	0	1	0	1
3. Moderate mental retardation (imbecility not accented)	1	0	1	0	1
4. Moderate mental retardation (imbecility accented)	1	9	0	10	10
5. Severe mental retardation	0	2	0	2	2
Total	8	11	7	12	19

The data about school attendance as an outcome variable were analyzed for elder study patients. There were 20 children at school age in the study group, and only 8 of them go to school.

From category “1”- 2 children;

“2”- 3 children , two of them go to special school (for retarded children)

“3”- 3 children, all 3 go to special school.

No patients attend kindergarten.

Risk factors

Late diagnoses and factors influencing on it

One of the primary risk factors for PKU patients' health outcome is late diagnosis and as a consequence the late diet initiation. It is proved by several studies that dietary treatment started within first 3 months of age is the most effective means for prevention of severe consequences of the disease (16) (13). Therefore, for each category of mental health the number of diagnosed patients in different time periods was estimated in this study. Only 6 out of 29 children were first screened within first 3 months of life, 5 of them are from the group with the best health outcome.(see Table 4)

Table 4. Distribution of age at the first diagnosis of PKU among patients with different outcomes.

	diagnosed in first 3 months		diagnosed in first 1 year		diagnosed in first 2 years		Total
Category of mental health	yes	no	yes	no	yes	no	
1. Normal mental development	5	2	6	1	6	1	7
2. Mild mental retardation (debility)	0	4	3	1	4	0	4
3. Moderate mental retardation (imbecility not accented)	0	4	0	4	2	2	4
4. Moderate mental retardation (imbecility accented)	1	10	6	5	7	4	11
5. Severe mental retardation	0	3	0	3	0	3	3
Total	6	23	15	14	19	10	29

According to data in Table 5 patients were mostly revealed and referred for screening by district pediatrician or neuropatologist, and neurorogenetics in Children Clinic.#6. But those who visited neurogenetics were referred by pediatrician. Thus, most often district pediatrician is the person who first refers the child to either Medico-Genetic lab for screening or to the specialists' office for consultation if the disease is suspected. In category "other" mainly patients with family history were included, when mother herself took the child for screening.

Table 5. Frequency of referral sources for the first screening of PKU detection.

Source of reference	Frequency	Percent
1. District pediatrician	5	17.2 %
2. Neuropatologist of district policlinic	7	24.1 %
3. Neurogenetist in Children Hosp # 6	7	24.1 %
4. Neuropatologist in hospital	3	10.3 %
5. Psychiatrist in hospital	2	6.9 %
6. Other	5	17.2 %
Total	29	100 %

The described finding lead to the idea that since there is no routine screening for PKU in Armenia, mothers awareness may be an important factor for early diagnosis of the disease. Some families who

applied for the first screening themselves, without physician's advice, because they had a Pku child before and they knew that the newborn child is also at risk for developing the disease. For this reasons data were analyzed to find out whether there is any relationship between having a PKU child in family before and early diagnoses of the disease.

Table 6. Early diagnosis connecting with family history of PKU.

	Have PKU child before		
PKU Diagnosed	yes	no	Total
< 3 month of life	4	2	6
> 3 month of life	4	19	23
Total	8	21	29

Data in Table 6 supports the above mentioned assumption. 4 patients out of 6 screened within first 3 months of life are from the families with an elder sick child. Half of patients from such families were diagnosed reasonably early time, while only for 2 out of 21 the first PKU children in the family screening was applied in that age (one of them was screened in Moscow). But in 4 cases parents didn't apply in the right time for the screening despite the knowledge about being at risk. Actually they were 3 mothers because 2 children are from the same family and this was the only family which had 3 children with PKU. Further analyses showed that all 3 moms had low knowledge and attitude scores. On the question "Do you think that the developmental delay is preventable for a child with PKU?" they answered "not preventable" or "don't know".

Early consultation of district neuropatologist was postulated as a factor which can potentially effect early diagnosis of the disease in this study. Table 7 shows that the majority of early diagnosed patients were early examined by neuropatologist (5 out of 6); and the majority of patients with late examination were diagnosed late (8 out of 9). The highest proportion of visits during the first 3 months of life is in the best outcome group and it is higher in the first three groups than in the last two (see Table 10 column4).

Table 7. Early diagnosis of PKU related to early consultation of neuropatologist.

	Age at first neuropatologists' visit	

Age at first diagnosis	= < 3 month	> months	Total
= < months	5	1	6
>3 month	15	8	23
Total	20	9	29

Not appropriate initiation of dietary treatment

Early diagnoses is important for early start of dietary treatment . For 25 children out of 29 the diet was changed connected with the disease, for 20 of them dietary treatment was initiated within 1 month after PKU diagnosis (see Table 10). Thus, for 4 children the diet was not altered. Two of them are in age 4 and 5 months, they are breastfed and included in the category of children without mental retardation. Two others are from the category 3, from the same family whose parents have inadequate knowledge and wrong attitude towards the preventability of the complications. One of patients in category "5" never received the special food, but since the parent said that the diet was altered it was considered that the child received the treatment.

Baseline level of Phe

One of the factors proved to affect mental health of PKU patient is concentration of phe at baseline. In this study results of the first blood screening were taken as a baseline level of Phe and no association was found between this factor and health outcome of the patients. Approximately the same proportion of children in different health outcome groups had baseline Phe level higher than the mean of the whole study group (the mean was 19 mg/%). Two explanations are suggested for this fact. First of all patients were diagnosed in different age. Level of Phe in PKU children highly depends on the diet in screening period. Thus, those who were diagnosed in breastfed period are supposed to have lower level of Phe. The next explanation is: the association could be observed if all patients receive the same medical care. Affect of baseline level of Phe is effaced with difference in health care management. This fact one more time shows the importance of health care for PKU patients health outcome.

Control and monitoring of the medical care

After disease diagnosis and dietary treatment initiation further follow up and monitoring is expected to influence health outcome of a PKU patient. For this reason definite activities were measured for different outcome groups. The results of analyses are presented in Table 10. More patients from the outcome categories “1”, ”2” and “4” visited the physician during last 6 months. The highest proportion for having a screening test during the same period is in group “1”.

Availability of the special phenylfree food

Data were also collected on availability of special phenylfree food at home during the last two weeks before the interview. Only 9 out of 29 patients had the food. Table 8 compares this factor with the level of phe during the same time period as a dependent variable. The analysis was performed only for those who undergone the screening during two last weeks before interview. In agreement with practice in Armenia level of phe 5 mg/% was used as the highest acceptable. Results of the analysis support hypothesis about dependents of phe level on diet, particularly on availability of the food.

Table 8. Dependence of phe level from availability of special phenylfree food during the last two weeks.

	Availability of food		
level of phe	yes	no	total
= <5	5	1	6
>5	3	8	11
total	8	9	17

Sources of information and knowledge

The appropriate follow up of the patients highly depends on parents’ ability to cope with the disease.

Knowledge of parents about health care management of PKU patients was measured. There were 5 knowledge questions in the questionnaire. The knowledge score scale was derived and mean knowledge score was estimated for each outcome group. The positive association between high

knowledge scores of parent and improved health outcome of the child was observed. (see Table 10, column 7).

Availability of information sources for parents other than the neurogenetist's office in Children Clinic #6 was higher in children with improved outcome (see Table10). Out of 11 cases who had such a source of information 9 are children in improved health categories "1" and "2". While specifying "which source" parents mentioned literature and medical workers in Russia whom they visited for consultation. Keeping a diet record can be considered as an indicator of the diet follow up and parents' accuracy in the same time. Out of 6 parents who ever kept a diet record 5 were from the first two categories of outcome (Table 10 columne 11).

Demographic factor

In the present study no much difference was revealed between patients of different groups in respect of the parents'' level of education and family income. Slight difference was noted for the groups regarding residency (table n). More patients from first groups than from the last ones are from Yerevan, all patients who live out of the country are from the first two groups. In existing conditions of Armenia (the only Medico-Genetic laboratory where PKU screening can be done and the only office which provides the special food are in Yerevan) residency must have been a strong risk factor for appropriate medical care for PKU patients. But in this study the association regarding residency and health outcome was not so strong which can be explained by the fact that patients in study population were only from regions close to Yerevan.

DISCUSSION

The study had variety of limitations;

- recall bias was possible for some questions, but it was compensated by the record review;
- the interview was performed at the hospital were patients are supposed to receive medical care, this fact may have an influence on answers of parents for certain questions;
- data regarding some variables was available for only part of the study patients;
- in some cases other relatives instead of moms came for the interview (fathers, grandmothers);

- patients of different age groups were included in the study, while the disease requires different medical care depending on age. For this reason it was difficult to measure some variables for the study group;
- small sample size.

It can be assumed that 29 children included in the study are in better situation than other PKU patients in Armenia, because they are the ones who attend the appropriate specialist, receive treatment and follow-up.

Only 24 % of PKU patients included in the study are mentally and physically normal developed. Together with mild retarded patients it forms 38 %. Thus, it can be stated that 62 % of patients under the study developed severe forms of retardation.

Despite the fact that the sample size didn't allow to make statements about the significance of findings, present study have some observations which are consistent with those of other studies. Important variables such as early diagnosis, timely initiation of dietary treatment, physician attendance, further screening for control were associated with improved current health status. Present study showed the relationship between parents' knowledge and successful treatment. Knowledge itself associated with additional sources of information. Family history of PKU contributed in better management and better outcome, but only in condition of parents' high knowledge and good attitude.

The group of normally developed children needs to be discussed separately. There are 7 patients in the group. Five of them are diagnosed earlier than 3 months of age, one child - in 4 months. For five of the patients the diet was initiated within 1 month after diagnosis, which tells not only about the early start of dietary treatment but also about parents' accuracy. Another two children are 4 and 5 months of age, they are breastfed and don't receive the special food. Though they are in good condition now it is early to make the final conclusion about their development. All patients of the group were under good control and follow up. Six out of seven had other sources of information.

An interesting observation was made about three patients of this group who had positive family history of PKU. They all were diagnosed within first week of life, they received the appropriate treatment and have satisfactory outcome. All elder PKU children in this families are retarded.

Two patients live in Russia, they receive medical care from the appropriate specialist. They also have additional sources of special food and information about coping with the disease.

One patient from the group is an unusual case. He was diagnosed very late, at 7 years of age, when mother came with the complaints on child's not attentive behavior in school. After diagnosis diet was altered. Now the boys health condition is normal, he attends the school. Benign PKU was diagnosed for the patient.

Three patients from the group with the most severe mental and physical developmental delay were also considered separately. They were poorly controlled and monitored, i.e. they rarely attended the specialist, had undergone unsatisfactorily screening and none of them ever had diet record. But the main finding was that they all were diagnosed after 2 years of age and their parents had poor knowledge on the disease management.

CONCLUSION

Taking into consideration existing means for diagnosis and health care provision to PKU children as well as health condition of the patients, the health care management of PKU patients in Armenia can be

assessed as unsatisfactory. This study observed the following risk factors that associated with health outcome of the patients.

- not appropriate system for diagnosis, absence of routine screening for newborns;
- insufficient provision of food
- poor attendance of physicians office;
- poor control by blood screening
- low knowledge of parents and lack of information for them about the disease;
- more than half of diagnosed PKU patients are not under the control of the specialist and probably don't receive any medical care.

Based on mentioned risk factors definite implementation strategies can be suggested. Taking into consideration limited opportunities of the country the strategies were prioritized in terms of importance and realization.

Table 9. Implementation strategies prioritized in terms of importance and realization.

more important	less important
- establishment of a new information sources for parents (brochures, lectures) - creation of the diet for patients (except the special food), availability of diet records - reaching the patients who are not under the control of the specialist	-special education for retarded PKU patients - information for pediatricians in the limits of any existing educational program
-establishment of routine screening for newborns -provision with the special food	- increasing attendance to the physician - increasing the control by screening

The implementation can be started from the most important and easy to implement strategies and then continued according to available budget.

Table 6 . Frequency of different variables for all categories of mental health in PKU patients.

		1. diagnosed < 3 months of life		**2.** diet ever initiated		**3.** diet in. within 1 month after diagnosis		**4.** neuropatologist consultation < 3 month		**5.** physician visit during the last 6 months		**6.** screening test during the last 6 months		**7.** knowledge scores (percent)
Category of mental health	freq	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no	
1. Normal mental development	7	5	2	5	2	5	0	6	1	6	1	6	1	68 %
2. Mild mental retardation (debility)	4	0	4	4	0	2	2	3	1	4	0	2	2	61 %
3.Moderate mental retardation (imbecility accented)	4	0	4	2	2	2	0	3	1	1	3	1	3	57 %
4. Moderate mental retardation (imbecility not accented)	11	1	10	11	0	9	2	6	5	10	1	6	5	50 %
5.Severe mental retardation (idiocy)	3	0	3	3	0	2	1	2	1	1	2	1	2	46 %
Total	29	6	23	25	4	20	5	20	9	22	7	16	13	46 %

	8. screening test within 2 weeks		**9.** acceptable level of phe during current screening		**10.** PKU child in family before this one		**11.** ever kept a diet record		**12.** sources of information except the physician		**13.** residency		
Category of mental health	yes	no	yes	no	yes	no	yes	no	yes	no	Yerevan	Armenian regions	out of country
1.	4	3	4	0	3	4	2	5	6	1	3	2	2
2.	3	1	1	1	0	4	3	1	3	1	2	1	1
3.	2	2	1	2	1	3	0	4	0	4	3	1	0
4.	7	4	0	7	4	7	1	10	1	10	3	8	0
5.	1	2	0	1	0	3	0	3	1	2	1	2	0
Total	17	12	6	11	8	21	6	23	11	18	12	14	3

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Information List for PKU Patients

My name is Nelly Tadevosyan. I am a pediatrician and I am conducting a survey about PKU patients. The survey will help us to understand better the problems you face when coping with your child's disease. Would you be willing to participate in the survey by answering a few questions? It will take only 10 minutes to complete.

1.Respondent # _____ 3. Location _____

2.Child's name _____ 4. Date of interview _____

5. Information about children in family (start from the oldest)

#	name of child	date of birth	have PKU (yes/no)
1.			
2.			
3.			
4.			
5.			

Tick the # of the child for whom the questionnaire is filled out.

child's name _____

#	Question	Parent's answer	Record review
6.	Date when PKU was diagnosed for the first time?	year ___19_____ month _____ day _____ don't know XX	year ___19_____ month _____ day _____ no information.....XX
7.	Where was the first blood screening for PKU detection done?	Med-Gen lab in Yerevan .....1 other _____.....2 don't know XX	Med-Gen lab in Yerevan .....1 other _____.....2 no information.....XX
8.	Who referred your child for the first screening? *(read all answers, tick only one)*	1. district pediatrician .....1 2. neuropathologist of district policlinic .....2 3. neuropathologist from hospital #_____ .....3 4. psychiatrist in hosp#____.... 4 5. neurogenetics in hosp#6.....5 6 . other_____ .....6 don't know XX	1.district pediatrician .....1 2. neuropathologist of district policlinic .....2 3. neuropathologist from hospital #_____ .....3 4. psychiatrist in hosp#____.... 4 5. neurogenetics in hosp#6.....5 6. other_____ .....6 no information.....XX
9.	What was the level of Phenylalanine during your child's first blood screening?	_____ don't know XX	_____ no information XX
10.	What was the age of your child when district neuropatologist sow him for the first time?	_____ years, _____ month don't know XX	_____ years, _____ month no information XX
11.	Was the diet of your child changed connected with the disease? 1. yes 2. no If yes when?	year ___19_____ month _____ day _____ don't know XX	year ___19_____ month _____ day _____ no information.....XX
12.	How many times did you visit your physician during last 6 month?	_____times don't know XX	_____ times no information.....XX
13.	The date of the three last screenings for phenylalanine in blood ? Start from the last.	1. ____/_____/_____ 2. ____/_____/_____ 3. ____/_____/_____ don't know XX	1. ____/_____/_____ 2. ____/_____/_____ 3. ____/_____/_____ no information.....XX
14.	What were the results of three last screenings for phenylalanine in blood? Start from the last.	1. _____ 2. _____ 3. _____ don't know XX	1. _____ 2. _____ 3. _____ no information.....XX
15.	Where does your child receive medical care for PKU mainly? *(read all answers, tick only one)*	1. district pediatrician .....1 2. neuropathologist of district policlinic .....2 3. neuropathologist from hospital #_____ .....3 4. psychiatrist in hosp#____.... 4 5. neurogenetics in hosp#6.....5 6. other_____ .....6 don't know XX	1.district pediatrician .....1 2. neuropathologist of district policlinic .....2 3. neuropathologist from hospital #_____ .....3 4. psychiatrist in hosp#____.... 4 5. neurogenetics in hosp#6..... 5 6. other_____ .....6 no information.....XX
16.	Have you ever had a notebook were you recorded food taken by your child. 16-1. If yes for how long time _____	1. Yes .....1 2. No .....2 don't know XX	1. Yes .....1 2. No .....2 no information.....XX
17.	Have your child ever had seizures ?	1. Yes .....1 2. No .....2 don't know XX	1. Yes .....1 2. No .....2 no information.....XX

Questions for parent\guardian.

Parent's knowledge, believes, attitude, sources and quality of information for him.

18. In your opinion what factors affect the health status of a child with PKU? *do not prompt, tick all answers*
    1. Age when diagnosed.
    2. Diet, food intake.
    3. Phenylalanine level monitoring.

4. Nothing.
5. Don't know.
6. Other _____

19. In your opinion does diet effect the health status of a child with PKU? *(read answers, tick only one)*
    1. Strongly effects.
    2. Effects.
    3. Does not effect.
    4. Don't know.
20. Do you think that the developmental delay is preventable for a child with PKU? *(read answers, tick only one)*
    1. Completely preventable.
    2. Partly preventable.
    3. Not preventable.
    4. Don't know.
21. How did your child's health condition improve after the diet therapy initiation? (*read answers, tick only one)*
    1. Strongly improved.
    2. Fairly improved.
    3. Not improved.
22. During your visits has your physician ever talked to you about what should your child eat?
    1. Yes
    2. No, (if no go to Q # 24)

23. If yes what did he/she tell you? *Don't read and tick all appropriate answers in the first column, then read all and tick only added answers in the second column.*

	Tick before prompt	*Tick after prompt*
1. Your child needs a special diet.		
2. The diet is very important for your child.		
3. The diet should be prescribed and controlled by physician.		
4. The diet should be controlled by screening the blood phenylalanine concentration.		
5. The diet could be changed with the time		
6. Meat mast be excluded from the diet.		
7. Your child can take limited amount of meat.		
8. Diet record keeping by yourself will be beneficial for your child.		
9. Other _____ _____		

24. Do you have any other sources of information about coping with PKU disease (except for you physician)?
    1. yes. If yes what _____
    2. no.

Availability of special food

25. Have you ever had special phenylfree food at your home during last two weeks (excluding the one you received today) ?
    1. yes
    2. no if no, when did you have it for the last time?_____
26. What kind of food was it?
    1. formula

2. other _____

27. Where did you get the food?
1. hospital # 6
2. other _____

28. Usually how do you know that neurogenetic's office have food for you?
1. Physician or nurse call me.
2. I call the hospital.
3. I call the physician's home
3. During visits to office.
4. other _____

Food intake

29. How many times during last week your child had following food and in what amount ?

Food	**# of times food taken**	**amount in each time**
1. meat		
2. milk		
3. yogurt		
4. cheese		
5. eggs		
6. cereals		

Food	**# of times food taken**	**amount in each time**
7. vegetables		
8. fruits		
9. green		
10. special phenylfree food		
11. other		

30. Does your child attends any children's institution ?

Yes.....1 If yes which ?
No.....2

1. School
2. Kindergarten
3. Special school
4. other _____

`

General information

31. What is the level of your education?
1. school 8 years
2. school 10 years
3. college / tecnicum
4. university
5. higher

32. Approximately how much money does your family spend during a month?

less than 20.000 drams (<$40)	
20.000 - 50.000 drams ($40-100)	
50.000 - 100.000 drams ($100-200)	
100. 000 - 150.000 drams ($200-300)	
more than 150.000 drams ($>300)	

Health Status of the Child.

Child's name _____

33. Conclusion of psychiatrist.

1. Child's mental development is normal.
2. Mild mental retardation (debility).
3. Moderate mental retardation (imbecility not accented).
4. Moderate mental retardation (imbecility accented).
5. Severe mental retardation (idiocy).

Current level of Phe

34. Date of last screening	____/_____/_____
35. Results of last screening	

Assessment of development level using Ireton Charts

36. Gross motor
    1. Normal
    2. Questionable

37. Language skills

    1. Normal
    2. Questionable

Other information about child's health.