Newborn PKU screening in Turkey: at present and organization for future

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SUMMARY: Özalp İ, Coşkun T, Tokatlı A, Kalkanoğlu HS, Dursun A, Tokol S, Köksal G, Özgüç M, Köse R. Newborn PKU screening in Turkey: at present and organization for future. Turk J Pediatr 2001; 43: 97-101.

At present, pkenylketonuria screening is a national child health program in Turkey which is carried out collaboratively by the Ministry of Health and three University Children's Hospitals in Ankara, İstanbul and İzmir. Since 1986 the number of cities included in the screening program has gradually increased, now and it covers all the metropolises the country. A total of 383 babies were found with persistent hyperphenylalaninemia (1:4172) among 1,605,582 babies screened by the Guthrie test at the Hacettepe Screening Center in Ankara. By taking into account pretreatment phenylalanine levels and phenlyalanine tolerances at five years of age, the numbers of classical and mild-moderate phenylketonuria and mild hyperphenylalaninemia cases were 216, 102 and 58, respectively.

The major problems encountered in the screening program and in management of the detected cases were unsatisfactory sample collection, early discharge from maternity hospitals, difficulties in reaching some detected cases, and noncompliance with dietary therapy due to illiterate parents or to lack of social insurance. To screen and treat all newborns for phenylketonuria and to include at least hypothyroidism in the screening program, there is a need for a more disciplinary intersectoral approach than exists at present.

Key words: phenylketonuria, national screening, screening problems.

Due to improvements in health services, and in environmental and socioeconomic conditions, the pattern of morbidity has changed significantly in Turkey. It can be clearly observed that preventable diseases such as infectious and nutritional disorders became minor problems, while other disorders such as inborn errors of metabolic diseases, congenital malformations and malignancies are listed among the most common diseases[1]. Thus it becomes very important to assess the magnitude of problems related to the above-mentioned disorders, to take preventive measures to decrease their incidence, and to screen for the ones that can be treated when diagnosed early.

Based on our clinical observations and then a pilot study we carried out in Ankara, the incidence of phenylketonuria (PKU) is quite high and screening for this particular disease needs to be considered a desirable part of preventive medicine[2,3]. Therefore we began in 1986 to screen newborn babies for PKU on a nation wide basis in collaboration with the Ministry of Health. We will report here the screening organization we have reached at present, some of our results, problems encountered thus far, and our proposed organization for a more effective mass-newborn screening in future.

PKU Screening Program at Present

The screening program at first covered newborns born in maternity hospitals in the metropolitan areas of 27 cities in Turkey. The number of provinces included in the program was increased gradually, and the program now covers all the metropolises in Turkey. At present

we have three PKU screening centers. In addition to Ankara, newborns born in 77 out of 80 cities in Turkey are currently being screened at the oldest and largest screening center in Ankara at Hacettepe University Children's Hospital. Infants born in İstanbul and in İzmir can be screened locally in the other two centers at the Department of Pediatrics, İstanbul University, İstanbul Faculty of Medicine and at the Department of Pediatrics, Dokuz Eylül University Faculty of Medicine. It is a national child health program which is being carried out collaboratively by the Ministry of Health and the above-mentioned universities. Collection of blood samples from the newborns is organized by the Ministry of Health. Laboratory costs of the screening in the beginning were supported financially by The Turkish Society for PKU and Allied Disorders. At present costs are partly supported by the Ministry of Health as well. There is a recently established foundation METVAK to cover the costs of therapy and management of the detected cases with PKU who do not have any insurance.

PKU Screening Results

Table I shows the newborn screening results of 1,605,582 infants from 78 cities using the Guthrie bacteriological inhibition assay. High pressure liquid chromatography (HPLC) is used for the quantitative phenylalanine (phe) determinations. For the classification of PKU pretreatment phe levels of detected cases and their phe tolerance around five years of age are taken into account[4]. Since we could not assess phe tolerance in detected cases too young to be evaluated, results of newborns screened after June 1998 are not included in this Table. A total of 383 babies were found to have persistent hyperphenylalaninemia. (HPA) (1:4172). Three hundred and eighteen out of these cases were diagnosed as having PKU (1:5049). Two hundred and sixteen out of 318 cases with PKU were classified as having classical PKU and 102 cases as having mild-moderate PKU. Only 58 cases had mild HPA and did not need any diet therapy. Interestingly, initial serum phe levels were around 10 mg/dl in a few patients who were fed solely by breast milk. Blood phe levels of these patients, however, increased to levels compatible with classical PKU. These cases point to the fact that there might be similar cases in countries like Turkey were sole breast-feeding is a common practice in the first months of life. In fact, Berlin et al.[5] also reported similar cases with PKU.

Table I. Incidence of Hyperphenylalaninemias (HPA) in Turkey (n: 1,605,582)*

Type of HPA	No of detected cases	Incidence
PKU	318	1/5049
Classical	216	
Mild-Moderate	102	
Mild HPA	58	
Defect in BH4 Metabolism	7	
Total	383	1/4192

* January 1986-June 1998
False positivity: 0.4%

We have rather recently begun to routinely screen detected cases for BH_4 deficiency. The frequency of this type of HPA seems to be at least two percent, which is comparable with the incidence of BH_4 deficiency in some other eastern countries. In earlier reports it was also indicated that BH_4 deficiency is not rare in Turkey[6,7].

False positivity was 0.4 percent. Since neither false positive nor false negative results were observed in the unknown samples periodically sent from Germany for interlaboratory quality insurance, it was thought that false positivity was due to the contamination of the cards during sampling.

Turkey seems to have the highest PKU incidence, next to Ireland, when the results of the present survey were compared with those obtained in other countries[8-12]. The rate of consanguineous marriages among the parents of the persistent HPA patients was 45 percent, almost twice the current figure given for Turkey[13]. Presence of no consanguinity in more than half of the families, however, may reflect the high frequency of mutations in the phenylalanine hydroxylase (PAH) gene in Turkey. Carrier testing of 209 individuals supports the high mutated gene frequency hypothesis in Turkey[14].

Problems Encountered in the Screening Program

We have faced a great number of difficulties which prevented our reaching in total the objectives of the screening program (Table II). First, some health personnel do not yet consider neonatal screening as a part of preventive medicine, a fact that results in poor blood collection. Second screening specimens are not

being collected from about 40 percent of the 1.3 million deliveries yearly which do not take place in hospitals. In fact, most newborns are discharged within 24 hours, some even a few hours after delivery. Since not all babies have the opportunity of a second test, some cases may be missed. In recent years, however, some actions. Have been taken to motivate parents and to stimulate health personnel. At present, coverage has reached 54 percent of all the deliveries, and the percentage of babies having a second test has increased.

Table II. Major Problems Encountered in the PKU Screening Program

1. Poor collection
   - low percentage of coverage
   - inadequate sampling
   - late arrival of the blood samples at screening laboratories
2. Reaching the positive case late
   - ignorance of health presonnel and of the parents
   - incorrect or incomplete address
   - difficulties in the transport of the samples to screening laboratories
   - lack of intersectoral approach
3. Problems related to the follow-up of the affected cases
   - illiteracy and ignorance of the parents
   - limited number of experienced centers for the treatment and follow-up of the cases with PKU
   - difficulties in the supply of low-protein and low-phenylalanine products

Incomplete, incorrect or even non-existent addresses and lack of information among families about the importance of screening for abnormalities resulted in difficulty in finding some of the patients with positive screening results and in a relatively long interval between initial sampling and the onset of therapy. In fact, in around 15 percent of detected cases, therapy could not be initiated until after the first months of life.

Illiteracy as well as ignorance of the parents decrease the rate of compliance with the rigid and long-term dietary treatment[15,16]. Difficulty in obtaining special formulas and low-protein products locally and the low income of the families who are not insured have been the other problems we encountered in follow-up of the detected cases. Furthermore, general practitioners, even most pediatricians, lack experience in the management of PKU, and dietitians are not present in every hospital. At present we have only a few experienced centers for PKU cases. These are located in central and western regions of the country, and some of the patients cannot attend these centers as frequently as necessary. Consequently, owing to all the above-mentioned factors, it has been difficult, sometimes impossible, to keep the phenylalanine levels of detected cases within normal limits. The percentage of patients with good metabolic control was 92 percent in the first year, but dropped to 62 percent at the end of the second year. Only 51 percent of the cases who completed six years of therapy were found to have good metabolic control (Table III).

Tablo III. Quality of Dietary Control in PKU Patients (n: 123)

Duration of good metabolic control*	No of patients	%
For the first year	113	92
For the first two years	76	62
Through treatment period	55	45

* Average plasma phenylalanine level is ≤ 6 mg/dl.

Proposed Mass-Newborn Screening Organization for the Future

In the beginning we decided that in countries like Turkey with socioeconomic limitations and complicated demographic and geographic conditions, it was more important to start and develop a neonatal screening program without waiting until all of the conditions required for a very comprehensive program were met. It has been so, and since, 1986 the number of cities included in the screening program has gradually increased to at least cover newborns born in maternity hospitals in metropolitan districts in all cities in Turkey. In spite of all the problems encountered, we believe that implementation of the PKU screening program in Turkey has been accomplished. However, to screen all newborns for PKU, and to include at least hypothyroidism into the screening as well, there is an urgent need for a more disciplinary intersectoral approach. To achieve this, we propose organization as outlined in Figure 1, taking into account the problems we encountered thus far, health care structure and the socioeconomic conditions of the country.

Because the newborn population to be secreened is large, there should be regional screening laboratories, at least one in each geographical region of the country. To provide frequent

follow-up of identified cases there is an urgent need for specialized pediatric departments, at least one in each geographical district of Turkey. Since Turkey has financial limitations, screening laboratories could be placed in pediatric departments. Personnel involved in the screening program can be trained by pediatricians, dietitians and laboratory personnel in centers which already exist.

infants born at home. They can take part in the management of detected cases locally as well. Sample collection for second testing could also be made by midwives who work at mother and child health (MCH) centers in the cities.

At present prenatal diagnosis is performed only in the pregnant mothers with a previous PKU child and with informative molecular findings and on condition that the costs of the procedure

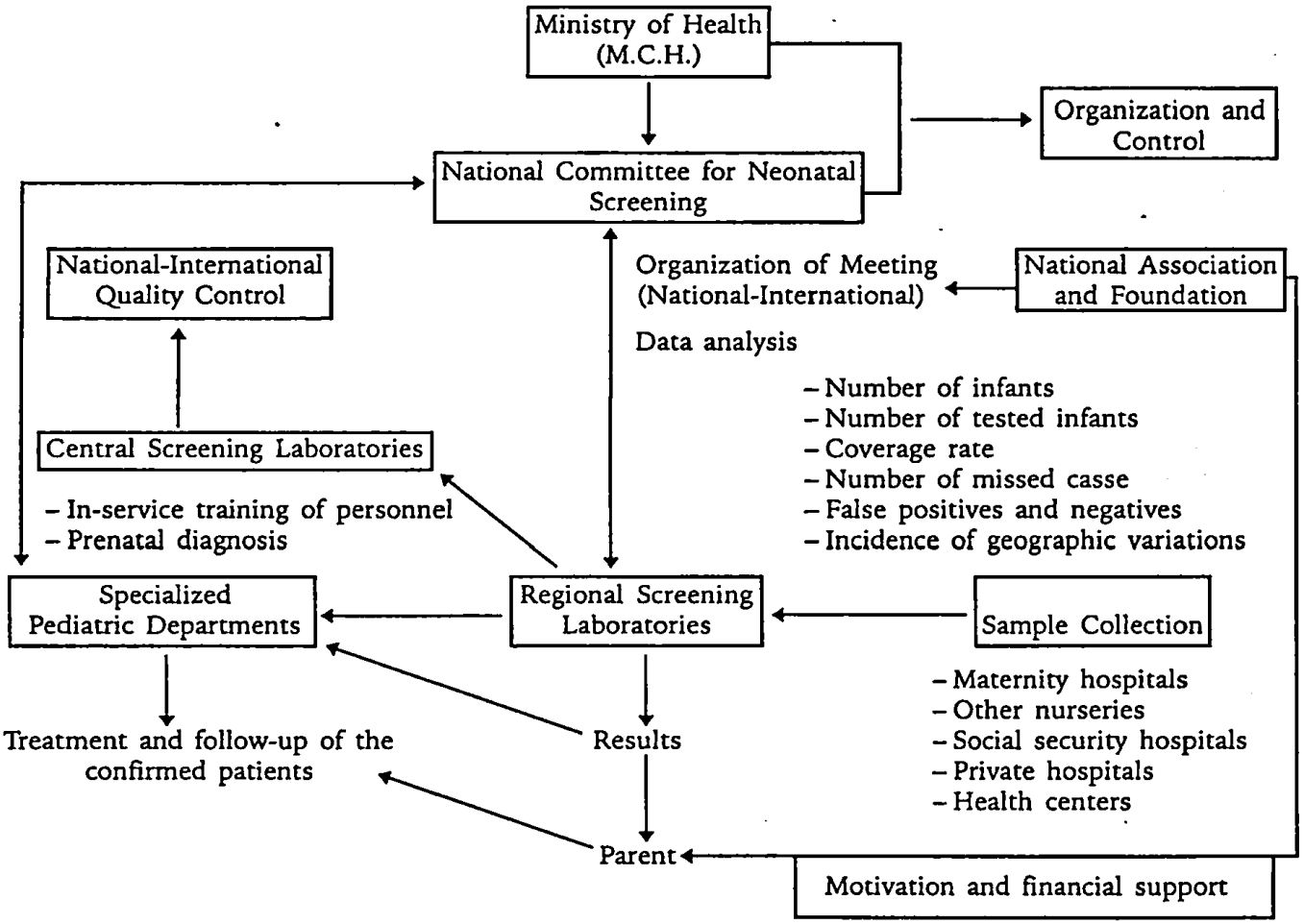

Fig. 1. Proposed neonatal screening organization for Turkey.

One of the essential components of the neonatal screening program should be national and/or international interlaboratory quality control. National interlaboratory quality control can be carried out in the screening center at Hacettepe University Faculty of Medicine that has already been under the control of the international quality assurance program in Germany[17].

In rural areas of Turkey, community-based midwives are the health personnel in close contact with the mothers. The screening program could be organized so that these midwives collect blood samples from the all

are met. Since the dietary formulas are very expensive and since at present one fourth of the mothers are not educated enough to follow rigid and long-term dietary therapy, prenatal diagnosis of PKU should be integrated into the screening program on a large scale. Molecular studies for prenatal diagnosis could be made in reference screening centers.

Pilot studies that have been carried out for hypothyroidism, biotinidase deficiency and galactosemia indicate that their incidence rates are also high[18,19]. We do not yet have any figure about the incidence of medium chain acyl-CoA

dehydrogenase deficiency, glutaric aciduria, maple syrup urine disease, or homocystinuria, which may also benefit from early diagnosis[20]. In fact, the organization illustrated in Figure 1 can be modified to allow additional screening for the above-mentioned diseases. Except for hypothyroidism, however, before conducting such a large-scale screening program for the other metabolic disorders, cost-benefit analyses should be made taking into account Turkey's present socioeconomic conditions.

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