Phenylketonuria in South Africa

A report on the status quo

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During the 1980s a pilot newborn screening programme for the early detection (and treatment) of amino acidopathies, especially phenylketonuria (PKU), was conducted by the Department of National Health and Population Development. The motivation for this pilot programme was the high priority accorded PKU screening in Europe and North America and the presumed similarly high incidence of this condition among South Africans of European origin. From a cohort of 59 600 newborns screened in the Pretoria area over a period of 8 consecutive years (1979 - 1986), only 1 case of PKU (and 1 of tyrosinaemia) was found. Statistically this result is compatible (Poisson distribution, 95% confidence interval) with a 'true' incidence of *not more than* 3/59 600 (or about 1/20 000) newborns. It is concluded from this result and other relevant information that newborn screening for PKU and other amino acidopathies is not cost-effective and justifiable, especially against the background of prevailing demographic conditions and more pressing health priorities in South Africa. This particular screening programme was discontinued in 1986. The results and conclusions are presented here for the record.

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Phenylketonuria (PKU) is a well-known, inherited metabolic disease. It has attained a high profile in the context of medicogenetic preventive services: because, among other reasons, it is known to cause severe and irreversible mental retardation;[1,2] its incidence among newborns in western Europe and North America is such that it warrants interventional programmes (Table I); it can be diagnosed pre-clinically by means of neonatal screening and subsequent specific laboratory tests;[1,3-5] and its serious sequelae, including mental retardation, are preventable by early dietary treatment.[2,6] Before the advent of newborn screening programmes for the prevention of PKU, relatively high numbers of patients in centres for the mentally handicapped owed their institutionalisation to this genetic disease.[7-9]

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Table I. Incidence of PKU in some countries/populations, as relevant for South Africa[1,16,23]

Austria	1:8 200	Scotland	1:6 000
Australia	1:9 000	The Netherlands	1:17 000
Belgium	1:6 000 - 8 100	New Zealand	1:16 000
England	1:19 000	USA (whites)	1:14 000
Ireland	1:4 500 - 7 700	USA (blacks)	1:50 000

Comprehensive and effective newborn screening programmes for the prevention of PKU began to be implemented on a state- (Massachusetts, USA) and country-wide scale in the early 1960s. These have in the meantime become accepted generally as part of routine primary health care services in many countries, where this has been recognised as a cost-effective and affordable priority. The impact of such screening programmes over time has been to reduce dramatically the incidence of new cases of PKU in mental institutions, e.g. in the USA and Canada.[10,11]

The white population of South Africa is primarily of western European origin with its well-known, relatively high incidences of PKU (Table I). It was therefore a plausible working hypothesis that PKU should be as common among the descendants of the European immigrants to South Africa, as among their populations of origin. This implied that it would be worthwhile to consider implementing a pilot newborn screening programme for investigating the cost-effectiveness and feasibility of more formal and comprehensive screening programmes for the prevention of PKU in South Africa, if found to be warranted. The first PKU screening programme in South Africa was launched in Johannesburg and continued for about 3 years (1964 - 1967) (personal communication — Johannesburg City Health Department, 1989). The test procedure comprised the Phenistix test on urine specimens of babies aged approximately 2 - 3 weeks (first test) and 6 weeks (repeat test). These were performed by health visitors in private homes. In total, about 36 000 babies underwent the first test and about 30 800 both tests; these were performed mostly on white (about 90%), but later also on brown and Asian babies (about 10%). Although some babies were found to be 'positive' or to have an indeterminate result on the screening test, these results were not confirmed on subsequent specific tests. Hence, no PKU baby was diagnosed from this screening programme (and no 'missed' cases were subsequently detected from this cohort of newborns). However, as is well known today, the Phenistix technique is insufficiently sensitive and many positive PKU cases may be 'missed' by this test. The point was also made that the Johannesburg screening programme had not convincingly ascertained the incidence of PKU in South African whites.[12]

Against this background it became more important at that time again to address the question of the incidence of PKU in South Africa, and to explore strategies required for its prevention, if found justifiable. For the period 1979 - 1981, Genetic Services of the then Department of Health and Welfare embarked on an exploratory neonatal screening programme, *inter alia* for the detection of PKU. This was then superseded by a more formal screening programme (February 1981 - October 1986). The present communication presents the results of these screening programmes for the sake of the record, and attempts to establish the most likely incidence of PKU in South African whites. As will be shown, the results do not justify a newborn screening programme for PKU in terms of cost-effectiveness and other competing health priorities in South Africa. A tentative alternative option to newborn screening, i.e. appropriate and specialised preventive services for high-risk PKU families (as is the case with many other genetic diseases), is presented for consideration.

Subjects and methods

For logistical reasons it was decided to implement the screening programme in the Pretoria area, and to concentrate initially on white babies because of the suspected higher incidence of PKU within this population group (see Discussion). It was endeavoured, as a matter of routine, to include all consecutive (unselected) babies delivered in the five maternity clinics serving the selected area. As required for PKU (and other feeding-dependent metabolic disorders), the blood specimens were taken at 3 - 5 days of age, by way of heel-prick and blood-spotting on standard filter paper cards. The collection technique, handling, storage and testing procedure complied with the requirements of the adopted methodology. The laboratory assay was usually done within a week of collection, and entailed the standard thin-layer chromatography (TLC) technique for the detection of phenylalanine (for PKU), and other metabolites for the detection of a variety of other amino acidopathies. TLC performed for this purpose and as an equivalent alternative to the Guthrie test was the method of choice at that time,[13] as also used in the screening laboratory at Great Ormond Street Hospital for Sick Children, London (where one of us, C.E.N., had obtained first-hand laboratory experience).

The regulations of the then Department of Health and Welfare (as well as of the subsequent Department of National Health and Population Development) require tender quotations for the laboratory tests, to be done according to accepted specifications. The successive tenders (renewed at intervals of 2 years) were awarded first to one particular private pathology laboratory (for the duration of the exploratory phase: 1979 - 1981) and thereafter to another one (1981 - 1986), both in Pretoria. The major part of the latter, formal phase of the screening programme was conducted under the technical supervision of one of us (C.E.N.). The sampling and laboratory procedures have also been discussed in greater detail in the context of screening for congenital hypothyroidism.[14]

Results

During the exploratory phase (1979 - 1981) approximately 14 000 newborns were screened for PKU and other amino acidopathies (as well as congenital hypothyroidism). Within this period 1 case of PKU was diagnosed clinically in

Pretoria. On checking this patient's record it was discovered that she had been tested as a newborn and found negative at the very beginning of the experimental screening phase (September 1979). She therefore represents a false-negative or 'missed' case.[15] During the more formal continuation of the screening programme at the second private pathology laboratory (1981 - 1986), another 45 600 newborns were screened and no cases of PKU were found. Private paediatricians in Pretoria, as well as the Department of Paediatrics of the University of Pretoria, were generally aware of the screening programme. It was expected that any 'missed' cases would come to the attention of their respective practices/clinics, as had been the case during the exploratory phase.[15] However, no further 'missed' cases of PKU came to our attention during the subsequent years. Of the other amino acidopathies screened for, only 1 case of tyrosinaemia was found among the cohort of 45 600 newborns.

Discussion

From the results as presented it follows that 1 PKU case was born from among some 14 000 newborns (experimental phase) and none was found among the 45 600 subsequent newborns of the second phase. On statistical analysis using the Poisson distribution, it follows that a combined incidence of 1 PKU case found in 59 600 newborns is compatible (within the 95% confidence interval) with a 'true' incidence of not more than 3 such cases from among that number of newborns.

From the screening experience evaluated here, the tentative conclusion is that the incidence of PKU in the Pretoria area (and possibly among South African whites in general) seems to be considerably less than in their European populations of origin. The incidence of PKU in South African blacks, browns and Indians has yet to be determined. Screening data on black and Indian populations in other countries[1,16] show PKU to be considerably less common in these racial groups than among whites. From local clinical experience, tentative observations (informal personal communications) suggest that while white PKU patients are occasionally seen, only 1 black patient has been diagnosed in this country.[17]

Whereas biochemical screening surveys of inmates of institutions for the mentally handicapped in western Europe and North America before the advent of newborn screening and prevention showed PKU to be the most common of such metabolic disorders (1 - 3% of all institutionalised patients[7-9]), the equivalent incidences for this country are far lower. Biochemical screening surveys at two large and representative South African Care and Rehabilitation Centres for white patients gave the following results: (*i*) Potchefstroom/Witrand: 1 568 patients screened, 1,29% found to have a metabolic disorder and 0,13% (2 patients) PKU;[18,19] (*ii*) Cape Town/Alexandra: 1 087 patients screened, 0,6% found to have a metabolic disorder and 0,28% (3 patients) PKU.[20]

A similar screening programme at the Rand West (Millsite) institution for mentally retarded black patients showed that of 267 patients screened, none had PKU and only 1 had a detectable metabolic disorder.[21]

The tentative clinical observations, as well as the data from mental institutions summarised above, support the conclusion drawn from the results of the newborn screening programmes presented here. PKU seems much less common among whites than elsewhere, and particularly rare among blacks, browns and Indians of this country (Table I).

Given the above conclusion it was decided that screening for PKU for any population group in South Africa was neither cost-effective nor justifiable, especially against a background of other, more pressing health priorities. The newborn screening programme for PKU and other amino acidopathies was duly discontinued in 1986 and no such programme is currently being conducted in South Africa (as far as we know).

Over recent years as many as 20 PKU families, each with one or more affected children of different ages, have been identified by anecdotal case finding (Genetic Services — unpublished data). These represent high-risk families with a known recurrence risk for PKU of 1 in 4. Such case-finding and identification of at-risk families (as routinely done for many other genetic diseases) provides opportunities for the prevention of recurrences. This conventional strategy is therefore an alternative option for identification of PKU in South Africa in the absence of routine newborn screening. The objective is to make appropriate information and comprehensive genetic services, such as the following, directly available to the families concerned, for their voluntary utilisation: (*i*) ongoing clinical evaluations, genetic counselling and dietary guidance for all affected (including pregnant) PKU patients and their families; (*ii*) the option of having molecular-genetic investigations done for the diagnosis of the underlying genetic defect and for the detection of heterozygous carriers in as many family members as would wish to avail themselves of this option;[22] (*iii*) voluntary carrier tests on (would-be) spouses of identified PKU heterozygotes; (*iv*) the option of a prenatal test for the diagnosis of an affected fetus in high-risk PKU pregnancies; (*v*) the offer to have newborn screening tests done on all babies born to these (extended) families; and (*vi*) guidelines for the dietary treatment of an affected baby (as identified by the abovementioned individual newborn screening test).

The comprehensive, preventive genetic service as outlined above is in keeping with what is being offered for many other genetic diseases worldwide. PKU in South Africa therefore reverts to the status of such a 'conventional' genetic disease. It is suggested that the recommended approach provides an appropriately effective alternative option for the prevention of PKU (given the local circumstances and the present level of laboratory expertise), in the absence of any large-scale newborn screening programme in South Africa.

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