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NEONATAL SCREENING FOR HYPOTHYROIDISM IN THE NETHERLANDS

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Contribution to the workshop on neonatal screening for hypothyroidism at the annual meeting of the European Thyroid Association, BERLIN, September 1978

by
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Neonatal screening for hypothyroidism in the Netherlands

As in many other countries, a beginning has been made for screening for congenital hypothyroidism (CHT) in the Netherlands.
One of the most important preparations for this screening was an investigation of the Dutch Pediatric Association of the incidence of CHT and the age of onset of treatment. The results of this investigation indicated the real need for early screening.
In order to initiate this project, a national committee for screening for CHT was instituted in 1976.
In 1978 the screening started in a defined pretest area and is being supervised by a regional committee, the 'Committee for screening for CHT in Rotterdam and surroundings' (chairman Dr. H.H. Cohen).
The results of the studies in this area will be discussed in the national committee and will determine how the screening in the Netherlands will be performed in the future.

In this paper the investigation of the incidence of CHT will be discussed (p. 3) and also the method and preliminary results of the screening in the pretest area (p. 6).

Abbreviations used:

T4	thyroxine
T3	tri-iodothyronine
TSH	thyroid stimulating hormone
TRH	thyrotropin releasing hormone
TBG	thyroxine binding globuline
FTI	free thyroxine index
PKU	phenulketonuria
CHT	congenital hypothyroidism

I. Incidence of congenital hypothyroidism in the Netherlands (1,2)

At the end of 1975 a postal inquiry was conducted by the Dutch Paediatric Association amongst all the pediatricians in the Netherlands about all children with congenital hypothyroidism (CHT), born in 1972 up to 1974 inclusive. It is not unlikely that in this country all diagnosed patients with CHT are under regular control of pediatricians. The response to the inquiry was virtually 100 percent. The following data were collected on each patient: initials, sex, birth date, birth place, birth order, date of onset of treatment by substitution.

1. Incidence

The total number of diagnosed cases of CHT was 97. The difference between boys (38 cases = 39%) and girls (59 cases = 61%) proved to be significant ($p = 0.05$). Two patients (1 boy and 1 girl), born in foreign countries, were not included in the calculation of the incidence. The 95 patients born in the Netherlands resulted in a natal incidence 1 : 6260 or 16.0 : 100.000 live births. This figure corresponds very well with the incidence of CHT in North America and Canada. A correction must be made for incompleteness of data (e.g. the birth cohort 1974 had only reached a mean age of 18 months at the moment of the inquiry); this could possibly account for 2 or 3 additional cases. The distribution of the birth order of the patients was the same as for all children born in these three years.

2. Geographical distribution

The distribution per province was as follows (table 1):

Table 1: Distribution of CHT in 1972 - 1974 in the Netherlands per province

Province	patients	live births	incidence
Groningen	3	24.012	1 : 8.000
Friesland	5	27.392	1 : 5.500
Drenthe	0	18.505	0
Overijssel	3	48.067	1 : 16.000
Zuid.IJsselmeerpolders	1	1.818	1 : 1.800
Gelderland	6	74.284	1 : 12.400
Utrecht	7	37.362	1 : 5.300
Noord-Holland	17	91.608	1 : 5.400
Zuid-Holland	23	127.241	1 : 5.500

Province	patients	live births	incidence
Zeeland	6	14.488	1 : 2.400
Noord-Brabant	15	88.971	1 : 5.900
Limburg	8	41.203	1 : 5.200

There is possibly some difference between the Eastern part (Drenthe, Overijssel, Gelderland) and the rest of the Netherlands.

3. Age of onset of treatment

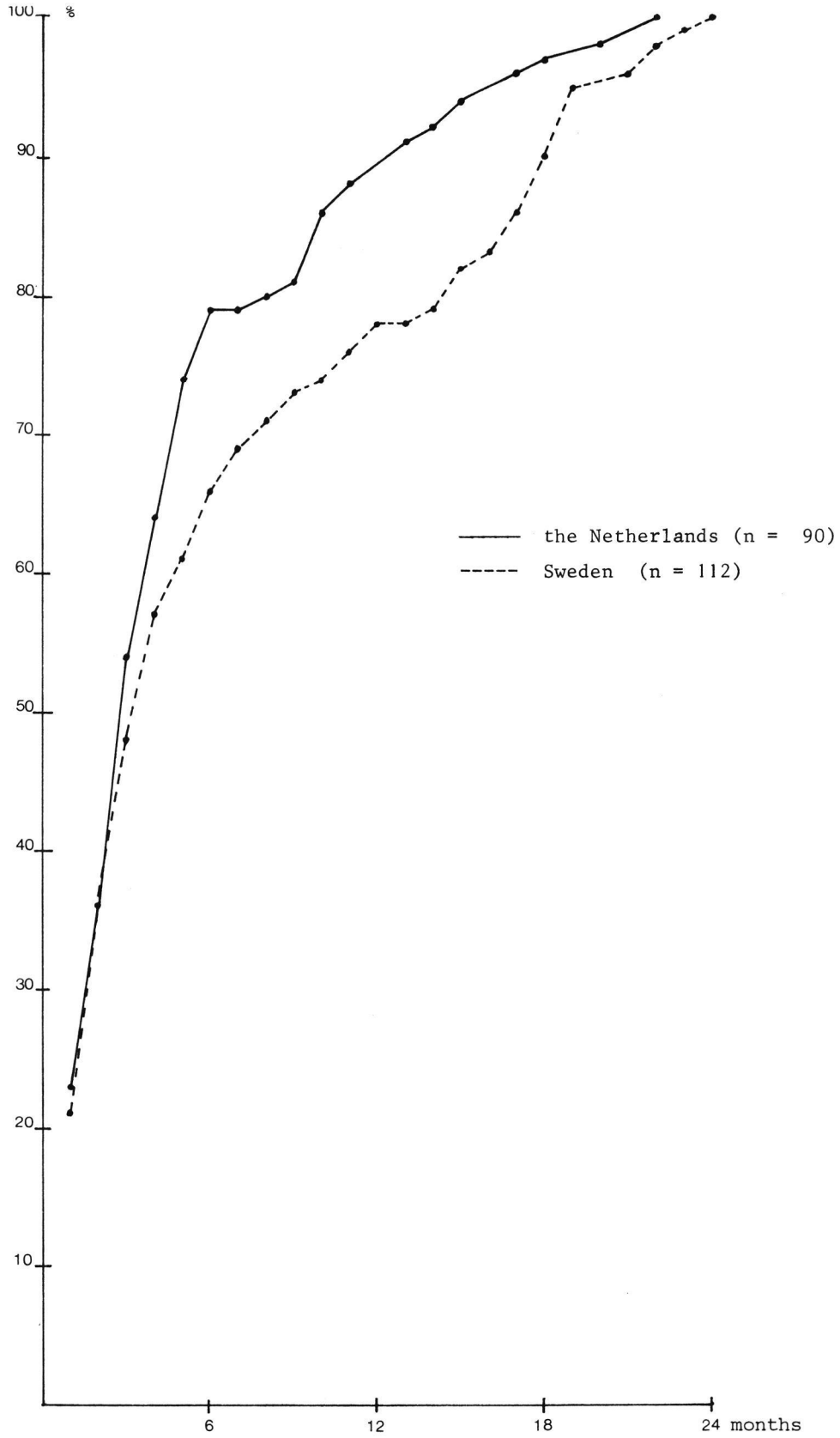
This age has been calculated from the reported birth date and the reported date of onset of treatment.

Table 2: Age of onset of treatment. Numbers and cumulative percentages

Age of onset of treatment	number	cumulative percentage
1 - 7 days	5	5.2
8 - 14 days	2	7.2
15 - 21 days	4	11.3
22 - 28 days	8	19.6
29 - 60 days	13	33.0
61 - 91 days	19	52.6
4 - 6 months	21	74.2
7 - 9 months	3	77.3
8 -12 months	6	83.5
2 years	11	94.9
3 years	4	99.0
4 years	1	100.0

Table 2 makes clear that the early diagnosis of CHT based on clinical signs and symptoms is uncommon in the neonate in spite of all medical control. In fact, the conclusion is that only 11.3% of all CHT-patients have been diagnosed in the first three weeks of life.
Comparison with a similar inquiry in Sweden (3) shows that the onset of treatment in Sweden of the infants diagnosed before the age of two years is about the same as in the Netherlands (fig. 1).
About 20% is under treatment at the beginning of the second month of life, about 50% at the beginning of the thirth month of life and about 90% at the first birthday.

Figure 1: Diagram of cumulative percentages of CHT (diagnosed before the age of two years) in the Netherlands and Sweden at the time of onset of treatment



4. Late effects

A previous study (4) (in 1971) of 46 CHT patients treated in Leiden showed that the prognosis of CHT is generally poor, also in the Netherlands. Only 34% in this group reached a normal intelligence (IQ > 90); 17% remained below the level of an IQ of 50.
The late effects of CHT on the mental health of the 97 patients in the present inquiry are still unknown. Nevertheless there is a need for longterm control and evaluation of the group of 97 children born in 1972 - 1974 to afford an unbiassed base of comparison for early screened patients in the future.

II. Screening for CHT in the defined pretest area

In order to have the opportunity to evaluate the screeningprocedure and the necessary organization, the national committee for screening for CHT decided to start screening in a limited area. Rotterdam and surroundings were eventually selected.
The number of live births in this area amounts to approx. 15.000 per year, therefore the expected number of CHT is 2 - 3 per year. The screening started 1 may, 1978.
In september 1978 the pretest area will be expanded and the number of births will then be 22.000; the expected number of CHT is than 3 - 4.
The number of live births in the Netherlands is approx. 170.000 per year.

In this paper the screening methods, organization, follow up approach and the preliminary results will be discussed.

1. Methods

In the defined pretest area we have followed the recommendations published in 1977 (5) by the Committee on Genetics of the American Academy of Pediatrics.

Measurements*) are done by radioimmunoassay from the eluate of blood spotted on filter paper, already collected for screening for PKU in the second week of life.
T4 is measured on all blood spots; for that purpose a punch is taken with a diameter of 3 mm from thwo bloodspots per child, and eluated.
Comparison of T4 values (n = 27) in serum and heelpuncture blood, collected at the same time, shows that the mean quantity of serum on a punch amounts to 0.97 microlitre.
The results are expressed in picograms/punch and in standard-deviations from the mean of the daily distribution.
If the T4 value belongs to the lowest 10% of the daily distribution TSH is estimated on the same blood specimen by punching a circle with a diameter of 6.5 mm around the original punch. Thus the mean quantity of serum for the estimation of TSH is about 3.58 microlitre/punch.
For the time being follow-up examination is performed if the T4 value belongs to the 3% lowest values of the day and/or of the TSH value is more than 0.08 microU/punch (approx. 20 mIU/litre serum).
With this method of screening we hope to detect not only the primary forms of hypothyroidism but also the hypothalamic-pituitary deficiencies that cause hypothyroidism.
These hypothalamic-pituitary deficiencies probably amount to 10 - 15% of all forms of congenital hypothyroidism, as described by Dussault e.a. (6).
At the moment in this pretest area, the selection percentage is 3%.
Possibly this percentage can be lowered after evaluation of the results.

2. Organization

An important reason for choosing for a combined CHT-PKU screening is the very high participation in the screening for PKU so far.

*) All measurements are performed in the Laboratory for Endocrinological Chemistry, (director Dr. W. Schopman), Bergwegziekenhuis, Bergselaan 62, Rotterdam, the Netherlands

Since 1974 99% of all live births in this country are screened for phenylketonuria. Blood collected by heelpuncture is spotted on filterpaper. In 98% the heelpunctures are performed in the second week of life. Since in the pretest area this screening has been combined with the screening for CHT, we have advised to do the heelpuncture in the beginning of the second week of life.

The heelpunctures are performed at home by the general practitioner, midmife, maternity nurse or district nurse, or, if the infant is hospitalized, in the hospital. The responsibility for the heelpuncture rests with the regional vaccination organization.

The parents are informed about the screening and asked for their consent in a information folder they receive at registration of the birth.

For those who perform the heelpunctures instruction meetings were held.

The filter papers are send by post to the laboratory, where the Guthrie tests for PKU are performed daily. This laboratory forwards those parts of the filter papers that are destinated for the screening for CHT to the appropriate laboratory.

The interval between the day of the heelpuncture and the day of the T4 measurement amounts approx. 2 days.

The physician of the vaccination organization receives information on the low T4 values 5 days per week and informs the family doctor. Although the TSH values are not yet known by that time, the infant should be referred for a follow-up investigation.

3. Follow-up

Every infant, whose T4 value does not exceed the lowest 3% level of the day, is referred for a follow-up investigation irrespective of his TSH value. The few infants whose T4 values are between the 3% and 10% level and whose TSH value is above the normal level of 0.08 microU/punch (> 20 mIU/l serum), are also referred.

Relatively many infants selected by the screening will be premature babies because no corrections of T4 values are made for preterm infants. The most of these will be hospitalized at the time of the screening and follow-up. Otherwise the infant is referred to the pediatrician by the G.P., preferably within a few days.

In a few cases, where the G.P. considers the distance to the hospital too far, the follow-up investigation is limited to taking a second sample on filter paper. In the defined area however, the follow-up investigation should regularly be done by a pediatrician.

The pediatrician will take a history and perform a physical examination according to the agreed protocol and send a serum sample for measurements of T4, T3, TSH, TBG-test (comparable to the T3 resin uptake) and FTI (T4 divided by TBG-test). If venepuncture fails a heelpuncture can be done. The follow-up investigation will be carried out in the outpatients department, of course with the exception of the examination of the infants who are hospitalized.
The infant is considered to be normal on the basis of the serum measurement, the history and physical examination.
The normal values we advise for infants in the third week of life are mentioned below. The values are based on the literature and our own experience.

Table 3: Range of normal and dubious values for the follow-up investigation for CHT in the third week of life

serum:	normal:	dubious:
T4	> 60 nmol/l	40-60 nmol/l
TSH	< 20 mU/l	20-50 mU/l
TBG-test	80-120%	
FTI	60-285	
T3	1.0-3.8 nmol/l	
Whole blood from filter paper:		
T4	> M-2.6 S.D.*)	
TSH	< 0.08 µU/punch	0.08-0,2 µU/punch

For preterm infants corrections have to be made.
If the measurements show doubtful values we advise a second follow-up investigation within two to four weeks.
Fig. 2 shows the diagram for the follow-up approach.
All pediatricians in the pretest area are participating in this protocol. The region covers 9 hospitals, each with one or two pediatricians and one academic centre in Rotterdam. From september 1978 the area will cover 7 additional hospitals.

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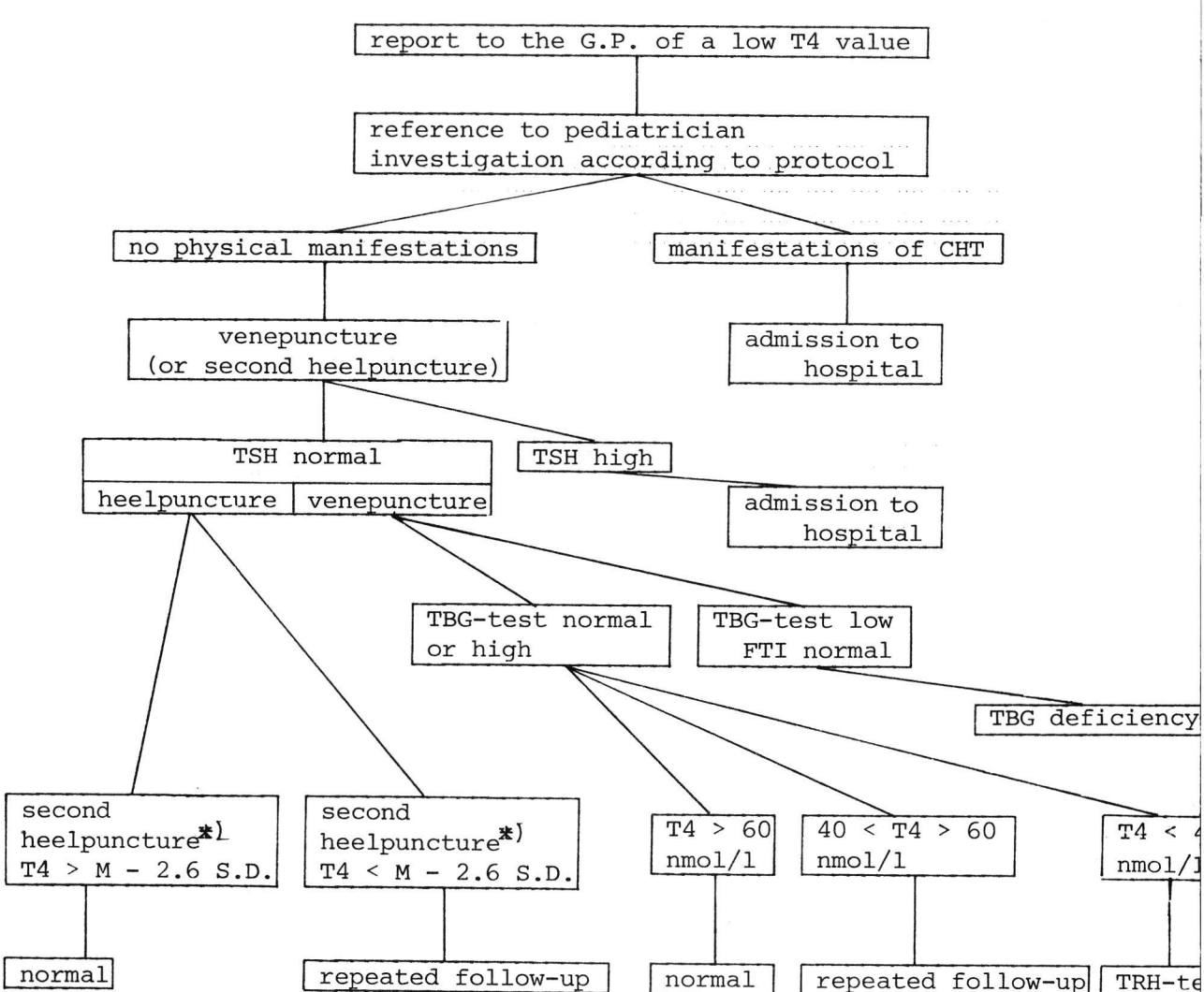
*) If a second heelpuncture is performed, the T4 value is compared to the T4 value found in the first blood spot. If the second value is lower than the first one, referral to a pediatrician is advised.

4. Problems

We have met two main problems in this screeningproject.
The first one is the high follow-up percentage of 3%. This percentage is considered to be too high for a national screeningprogramme. Evaluation of the laboratory techniques and results of the screening may indicate the possible reduction of this safety margin.

Figure 2: Diagram for the follow-up approach in the screening for CHT



*) See also footnote on page 9

The second problem is that we have insufficient knowledge about T4 values of preterm babies collected by heelpuncture in the second week of life. Research on this subject is necessary and has been started.

5. Preliminary results

From the start of the screening on 1 May, 1978 till 24 July, 1978 2844 T4 measurements on blood spotted on filter paper were performed. After the laboratory techniques had stabilized, the mean T4 value was 110,33 pg/punch (n = 2066). The distribution was nearly symmetrical (skewness 0.1) with a standard deviation of 19.7 and a kurtosis of 3.6. The mean T4 value per day did not deviate more than 10% from the mean T4 of the total distribution. The number of measurements per day varied from 25 to 100.

The values of 27 serum and heelpuncture blood measurements, collected at the same time, have been compared. A linear regression was computed: T4 in nmol/l serum = 1.33 x T4 in pg/punch - 0.6, with a correlation coëfficient of 0.74.

Up to 24 July inclusive 3.4% (95 infants) were selected for follow up, because of a low T4 value. Although the selection percentage chosen was 3%, the real figure was higher, because the number selected every day had to be rounded off upwards. All TSH values were under the level of 0,08 microU/punch.

No case of CHT has yet been found.

6. Finances

The screening in the pretest area is being subsidised by the Dutch Prevention Fund.

The follow-up is paid for by the sick funds.

Summary

Screening for congenital hypothyroidism in the Netherlands started 1 May 1978 in a defined pretest area.
An important preparation for the screening was an investigation into the incidence of CHT. A postal inquiry amongst all pediatricians about all children with CHT born in 1972 up to 1974 inclusive, showed an incidence of 1 : 6200 and showed also that only 12% of the infants was under treatment before the age of 4 weeks.
The chosen screeningmethod is measurement of T4 on blood spotted on filter paper, already collected for PKU screening in the second week of life. TSH measurement is performed on the same bloodspot if the T4 value belongs to the lowest 10% of the daily distribution.
In this pretest area the children whose T4 values belong to the lowest 3% and/or whose TSH values are above the normal level are referred for a follow-up investigation.
In nearly 3 months 2844 T4 measurements were done. No case of CHT has yet been found.

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