Audit of Newborn Screening Programme for Congenital Hypothyroidism

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SUMMARY

Newborn screening for congenital hypothyroidism (CH) was implemented in Hospital UKM in December 2004 using cord blood sample. From the audit over a period of 25 months, a total of 13,875 newborn babies were screened with a coverage of 98.8%. From this cohort, the mean recall rate was 0.32%; unfortunately the mean percentage of recalled babies that came for retesting was only 79.5%. In addition, the mean sample rejection rate was high, i.e. 2.2%. Two babies were diagnosed to have CH. These findings implied that whilst the coverage of screening was good, there is a need for regular surveillance of performance of both clinical and laboratory personnel. In addition, a more concerted effort should be carried out to promote community awareness of such a programme.

KEY WORDS:
Newborn screening, Congenital hypothyroidism, Cord blood

INTRODUCTION

Congenital hypothyroidism (CH) is a relatively common cause of mental retardation that is preventable. With the introduction of newborn screening programmes for CH, newborns with hypothyroidism are detected early before clinical manifestations are evident; this enables thyroxine replacement treatment to be instituted, ideally within two weeks of birth, thus reducing the risk for cognitive problems. Newborn screening for CH has been implemented in developed countries for the last three decades. Previously, glucose – 6 – phosphate dehydrogenase deficiency (G6PD deficiency) was the only disease that was screened for in Malaysia. In 2003 however, the Ministry of Health Malaysia, implemented a nationwide step-wise screening programme for CH for all babies delivered in the government hospitals. Following this, Hospital UKM embarked on a routine screening programme using cord blood for the screening of CH based on the ministry's guidelines.

MATERIALS AND METHODS

The objective of this study was to evaluate the efficiency of the screening programme for congenital hypothyroidism in Hospital Universiti Kebangsaan Malaysia (HUKM). This study is descriptive and retrospective in nature. Prior to the launch of the programme, community awareness and education was done via posters and distribution of information pamphlets to all expectant mothers booked at HUKM. This was carried out intensively six months prior to the commencement of screening. All newborns delivered in HUKM are subjected to cord blood testing for TSH (thyroid stimulating hormone). Daily census was obtained from the Labour Room to ensure that the list of registered babies was complete. All infants born through normal deliveries, Caesarean section and those born before arrival at the hospital (BBA) were recorded in a common registration book.

Newborns born before arrival at HUKM were screened via a venous blood sample obtained prior to discharge; this sample was taken as late as possible but if the baby was to be discharged within 24 hours, the sample was still taken. This was to ensure that all the newborns were screened. All blood samples (either cord blood or venous) were processed daily at the chemical pathology laboratory during weekdays; weekend samples were only processed on the following Monday. On a long stretch of public holiday, the blood samples were processed no later than 72 hours after collection to ensure that the results were not delayed. Cord blood TSH and total T4 were measured by standard laboratory methods on automated instruments i.e. Architect (Abbott Laboratories) and AxSym (Abbott Laboratories) respectively. All hormone testing was subjected to internal and external quality procedures with satisfactory performances achieved. A database was created and managed by an assistant medical scientific officer whose role was to liase between the laboratory and clinical staff. Recall and tracing of repeat samples was done by a paediatric clinic staff nurse. The standard operating procedure is as shown in Figure 1[1].

RESULTS

A total of 13,875 newborn babies were screened (including BBA) over the period of 25 months (Dec 2004 – Dec 2006); the mean coverage of screening was 98.8% (Table I). Of these, a total of 43 babies were recalled because of abnormal results; three had a TSH value of more than 60mU/l (range of 67.5 to 171.4mU/L) and the remaining 40 had TSH values which were within the borderline (25 - 60mU/l) category. Among this group of 40 babies, 24 had total T4 value of more than 100umol/L, 11 had total T4 of less than 100umol/L; the total T4 value of the remaining five babies was not analysed (Table II).

The mean screening sample rejection rate (RR) was 2.2% (total of 292 samples – Table II), of which the majority were the result of a haemolysed sample (276 samples: 94.5%); other reasons included wrongly labeled samples, inadequate amount of blood sample and even use of wrong specimen bottle. The trend of this rejection rate however declined since the start of the programme; i.e. in December 2004, the sample RR was 2.50% and in December 2006, it dropped to 1.2%.

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The recall rate (i.e. medical recall - as a result of abnormal values) for the year 2005 and 2006 were 0.25% and 0.39% respectively.

In 2005, of the 17 babies that had to be retested, 12 returned to HUKM for a repeat venous sample (70.6% - Table III). Of the remaining five babies (29.4%) that were not available for retesting, three were uncontactable, one was transferred to Hospital Mentakab for subsequent management and one opted to have the blood taken at a private practitioner. Whereas in 2006, of the 26 babies that required retesting, 23 (88.5%) had their repeat sample taken in HUKM; of the remaining three, one was uncontactable and the remaining two had their blood samples taken in Hospital Port Dickson and Hospital Pasir Putih respectively. The thyroid status for all those babies who had opted for retesting elsewhere were not followed-up.

For the group of babies that was recalled throughout the 25 months, the turnaround time (TAT) at three different points were looked at. First, at the laboratory service level (time frame from which the cord blood sample was taken to when the results, i.e. both TSH ± total T4, were completed) and second, at the clinical service (paediatric) level, i.e. time frame from when the cord blood results were available to the time when the results were reviewed by the paediatric team. The age when the baby returned for retesting was also reviewed (subject TAT). These various TAT were selected to reflect where possible delays could have occurred so that remedial efforts can be carried out in future.

Although the overall laboratory TAT for all screened babies was not available, the major concern was the unsatisfactory rate of TAT compliance for babies with borderline TSH results; 47% in 2005 (n=17) and 54% in 2006 (n=26). In this group of babies, although the median TAT was one day in each year, the longest TAT was ten days in 2005 which declined to six days in 2006. The main reason for the poor laboratory TAT was a delay in measuring the total T4 after obtaining a borderline TSH result. This is especially important since a significant proportion of babies with borderline TSH (60%) had a normal total T4 value (>100umol/L). Delay in the availability of the total T4 value could have contributed to unnecessary recall of babies for a repeat sample because in the majority of cases, the decision to recall the babies was based on the borderline TSH result before the total T4 result was known. Data for the clinical TAT was unfortunately incomplete. In 2005, data was only available for 7 of the 17 recalled patients of which the median time was within 24 hours. Similarly, in 2006 the median documented clinical TAT was also 24 hours. As for the subject TAT, the median was four days, with a range of 2 to 10 days in 2005 and in 2006, the median was three days with a range of 1 to 16 days.

As mentioned previously, two babies were subsequently confirmed to have CH; one had a cord blood TSH of 53.1mU/L (total T4 was 74umol/L) and the other a cord blood TSH of more than 100mU/L (sample insufficient for measurement of total T4 unfortunately). For the former case, thyroxine was commenced on day 12 of life whereas for the latter, on day 8 of life. One baby was subsequently diagnosed to have transient hypothyroxinaemia; this baby who was of foreign descent (Myanmar in origin) had a cord blood TSH of 67.5mU/L (but total T4 >100umol/L). A repeat venous sample on day 16 of life showed TSH more than 100mU/L and free T4 of 7.47umol/L; however, thyroxine was only commenced at day 21 of life. This patient subsequently defaulted treatment for over one year due to social reasons; however on the last follow – up, the thyroid function had normalized even without thyroxine treatment. Another baby whose cord blood TSH was 171.4mU/L (total T4 of 31.7umol/L) had a history of maternal thyroid disorder; results were normal on retesting.

DISCUSSION

Newborn screening is a form of population based screening which differs from conventional screening process in that it is non – voluntary i.e. all newborns are required to undergo the screening test. This is because the disease that is being screened has major health implication if not detected and treated early; such is the case with congenital hypothyroidism and several other types of inborn error of metabolism. Newborns with CH are generally asymptomatic and by the time clinical manifestations are evident (about six months of age), there is already irreversible cognitive impairment. Individuals with mental retardation pose a major health burden; thus, screening for CH has been shown to be one of the few programmes to have a positive cost benefit ratio[2].

Most developed countries utilize blood samples captured on filter paper (Guthrie), which are obtained beyond the first 24 hours of life. This is because T4 level is relatively low at birth and peaks at between 24 to 36 hours, whereas TSH level peaks at 30 minutes after birth and only declines to baseline values over the next 3 to 5 days[3]. This however, poses considerable logistic problems for certain countries where there is a practice of early discharge post – delivery (even before 24 hours). Furthermore, in Malaysia, most mothers tend to return to their rural hometown for the practice of confinement post delivery of up to 42 days and not all of these places have a dedicated public health nurse to obtain a filter paper sample. In view of these issues, the Ministry of Health implemented screening of CH using cord blood sample instead; this was convenient as there was already a screening programme for G6PD deficiency using cord blood in place since 1985. The main focus of this article is to evaluate the efficiency of this screening programme and to address the pitfalls that were encountered within our hospital.

This audit has generally shown a favourable uptake of neonatal screening as the coverage ranged from 98.5% to 99.0%, with an overall rate of 98.8%. This was in keeping with the Ministry of Health's quality assurance (QA) target indicator of achieving >99% coverage and indeed this is the essence of any screening programme, that is to ensure all newborns are screened. Our mean screening coverage also compares favourably with other developed nations, e.g. Western Australia (99%) and Scotland (99.9%)[2]. The (medical) recall rate for an abnormal TSH result ranged from 0.25 to 0.39% which again is in keeping with other screening programmes that adopt a primary TSH approach (reported to be between 0.03 to 0.8%); the MOH programme report (2001 till 2005) showed a range of between 0.6 to 0.9%[4]. The recall rate would also depend on the cutoff level of TSH that is adopted within any screening programme. In the United

Table I: Status of screening programme

Year	Total births (including BBA)	Number of Newborns screened (including BBA)	Percentage of births screened
Dec 2004	533	525	98.5%
2005	6790	6724	99.0%
2006	6716	6626	98.7%
TOTAL	14 039	13 875	98.8% (overall)

BBA = Born before arrival

Table II: Outcome of screening results

	Dec 2004	2005	2006	Total (or mean)
Live births	533	6774	6699	14 006
BBA	0	16	17	33
Samples screened	525	6724	6626	13 875
Rejected samples	13	200	79	292
Sample rejection rate (%)	2.5	2.9	1.2	2.2% (mean)
Normal TSH	525	6707	6600	13 832
Samples with high TSH (>60mU/L)	0	1	2	3
Samples with borderline TSH (25 – 60 mU/L)	0	16*	24**	40
Samples with borderline TSH (25 – 60 mU/L) and low T4 (<100umol/L)	0	4	7	11
Number retested	0	17	26	43
Recall rate for abnormal results (%)	0	0.25	0.39	0.32% (mean)

NOTE: In the above Table, the total T4 value was not analysed in 2* and 3** samples for each year respectively

Table III: Performance indicators for screening programme

QA indicator	Ministry of Health standard	Current performance		
		Dec 2004	2005	2006
Coverage at hospital level	>99% of births in hospital	98.5%	99.0%	98.6%
Screening sample rejection rate	<1%	2.5%	2.9%	1.2%
Duration of screening sample results to become available for subject recall \ (laboratory turn around time) in cases with borderline TSH results	<48 hours in 90%	*not applicable	47.0%	54.0%
Percentage of recalled patients seen for re-testing	100%	*not applicable	70.6%	88.5%

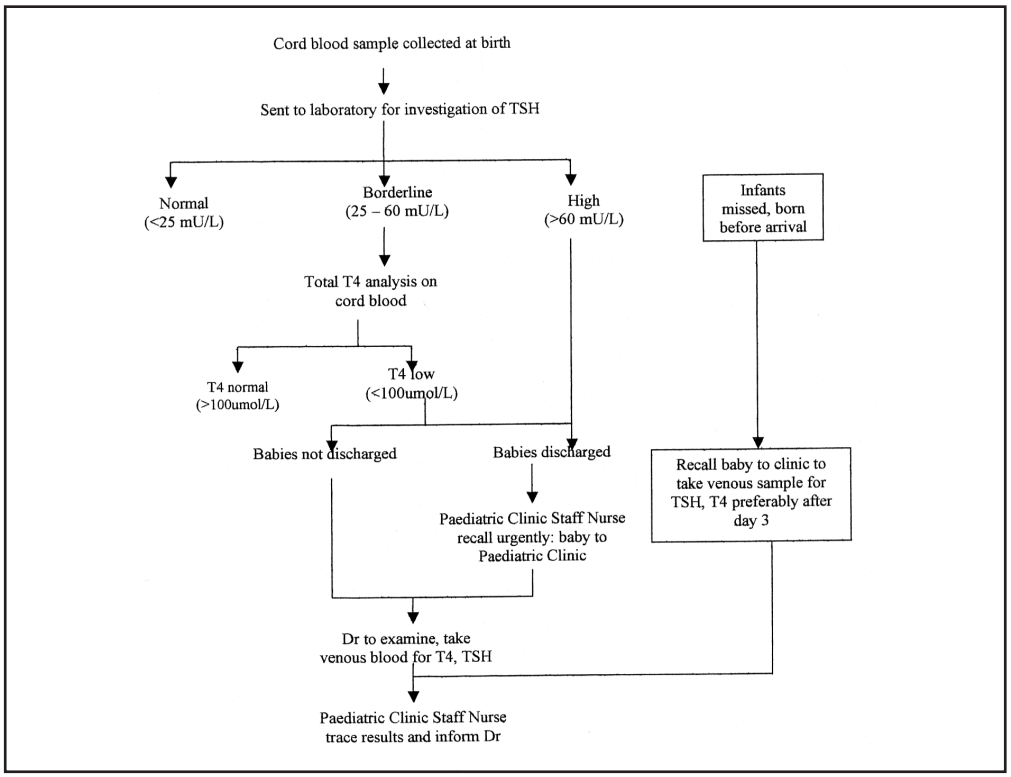

Fig. 1: Flow Chart for Screening of Congenital Hypothyroidism [1]

States, the recall rate was 0.65% and 2.6% for programmes that applied a cutoff TSH value of 25mU/L and 18mU/l respectively[5]. The use of cord blood is known to increase the rate of false positive screening results. In view of this, some programmes implement age-adjusted cutoff values to address this problem[5].

Our sample rejection rate, with a range of between 1.2 to 2.9% (mean of 2.2%), did not meet the MOH criteria of <1%[1]. The MOH programme report showed that their sample rejection rate was between 0.87% to 2.92% (mean of 1.47%) thus indicating that sample rejection is a universal problem[4]. A high sample rejection rate will result in unnecessary recall of newborn babies. Most of the samples (94.5%) that were rejected in our programme were haemolysed which probably reflected poor or incorrect sampling technique. Since the rejection rate declined as the programme progressed we can probably infer that the sampling technique improved with increasing familiarity of the procedure. Nevertheless, there still needs to be a continuous concerted effort in bringing down the rate even further.

The number of babies that had to be recalled could also have been reduced even further because not all of the newborns (20.8%) with a borderline TSH (as per guideline) had their cord blood total T4 level measured. This was the result of laboratory constraints and the fact that the guidelines were not made readily available to the laboratory counterpart. In addition, the two day laboratory TAT criteria was not clearly emphasised in the hospital guideline as seen in Figure 1.

The laboratory TAT was only achieved in 50.5% of babies with a borderline TSH result during the two-year period compared to the Ministry of Health's QA (Quality Assurance) target indicator of 90%[1]. It would have been ideal that this data was available for the entire cohort of babies that were screened. The maximum documented laboratory TAT for borderline TSH results was ten days which was due to a failure of the laboratory to identify the borderline TSH and a failure too of the liason personnel to follow-up on an incomplete screening report in that particular subject. This could have resulted in a delay in the recall of babies. Fortunately, in the majority of cases, the recall for a repeat venous sample was usually based on the TSH result alone. However, this practise contributed to an increased number of babies that were recalled unnecessarily. As for the subject TAT, the fact that there were cases who only came back for re-testing at ten days and beyond infers that there is a need for even more aggressive approaches in educating the public of this condition. Based on the Scottish screening programme, the median (range) interval between initial (Guthrie sampling) and final repeat sampling was 11 (1 to 52) and 14 (3 to 73) days in their 2006 and 1997 audits respectively[2,6]. Their results also indicate that delayed first-time sampling is an ongoing problem even though there was a decline in the time interval over the years; the delay in their cohort however occurred predominantly in the inpatient group[2].

The time taken for the two babies with CH to commence treatment was less than two weeks which is in keeping with the MOH guidelines[1]. However, the third case had only received thyroxine in the third week because the parents had delayed bringing in the baby for retesting (only at day 16 despite several reminders) and also failure of the clinical personnel to review the results of the repeat sample immediately. It is imperative that treatment is commenced as soon as possible; in order to achieve this certain measures may be adopted. This includes calling the babies back for blood sampling early in the morning and ensuring that the results and babies are reviewed at the hospital on the same day to avoid the parents having to bring the baby in for another appointment on a different day. The other alternative is to prescribe the baby with thyroxine and inform the parents the following day of the results so that they are able to institute the treatment as soon as possible. These strategies would avoid parents having to bring back their baby for yet another hospital appointment.

As mentioned above, from our cohort of 13,875 babies, two were confirmed to have CH. Based on the previously quoted incidence of 1 in 3,390, we would have expected four cases instead. This brings us to the issue of whether we have missed any case which is an important issue as there are medico - legal implications. There needs to be a national reporting system in place for cases that are missed as this will serve as a feedback system to ensure that the goals of the screening programme are achieved at all hospitals within the country, be it a government, university or private hospital.

CONCLUSION

This audit has shown a favourable uptake of newborn screening with an overall coverage of 98.8%. Two of the three newborns confirmed to have congenital hypothyroidism were treated within an acceptable time frame of two weeks; the latter case was subsequently diagnosed to have transient hypothyroidism. The mean recall rate was 0.32%, consistent with other screening programmes in developed countries. The high mean sample rejection rate infers poor sampling technique and the need for regular retraining of the respective medical personnel involved in the procedure. In addition, there needs to be an even better liaison between the laboratory and clinical personnel to ensure that both cord blood TSH and total T4 are measured within the specified time frame to optimise the recall rate. There should also be a more concerted and intensive effort to promote community awareness as only 79.5% of recalled babies returned for re-testing.

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