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"COST-EFFECTIVENESS ANALYSIS OF CONGENITAL HYPOTHYROIDISM IN NEONATES BORN IN UTTAR PRADESH: A PILOT STUDY"

[1]*Tiwari Vandana Ph. D, [2]Husain Nuzhat MD, [2]Awasthi P Namrata MD and [3]Pandey M. Chinta Ph. D.

[1]Department of Biochemistry, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP, India.
[2]Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP, India.
[3]Department of Biostatistics and Health Information, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, UP, India.

***Corresponding Author: Dr. Tiwari Vandana**

Department of Biochemistry, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP, India.

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ABSTRACT

Congenital hypothyroidism (CH) has long been recognized as a cause of mental retardation. Untreated, CH has devastating effects on growth and development of infants. Therefore present study was aimed to determine the incidence of hypothyroidism in neonates in our population and to determine whether a new-born screening for CH is cost-beneficial from a societal perspective. Heel puncture blood was obtained from neonates born in department of Obstetrics & Gynaecology at RMLCH after 48 hours of birth for screening of CH. Family history of thyroid disease, and other obstetric and relevant family history was recorded for each neonate. A commercial TSH assay was done for detection and specimens with TSH concentrations >20mIU/L were considered to suggest CH and additional follow-up testing was pursued. Incidence was estimated, costs for the detection and treatment of abnormality was compared to the projected benefits of preventing the mental retardation and consequent productivity losses. Out of 1210 neonates screened three were found positive for Congenital Hypothyroidism. Mother of two of these neonates was suffering from hypothyroidism and one was normal. The prevalence of Congenital Hypothyroidism in our study was 3/1,210 (approximately one per 400 live births during the period of study). Detection of CH with timely testing in neonates confirms the diagnosis and allows early treatment within a time frame that prevents mental retardation and maximizes a positive health outcome and quality of life.

KEYWORDS: Congenital Hypothyroidism (CH); Thyroid Stimulating Hormone (TSH); Disability Adjusted Life Years (DALYs).

INTRODUCTION

Congenital hypothyroidism (CH) is one of the most common among the preventable causes of mental retardation in children. The worldwide incidence of CH is 1:3000 to 1:4000 live births[1], while in India very few such studies have been done and incidence varies across the states. Incidence of 1:2500-2800 and 1:3400 live births from North India[2,3] while reports from Southern part where the most common cause is thyroid dysgenesis incidence was 1:500 which is at least eight times higher as reported in western literature[4], and from eastern part it is reported to occur with an incidence of 1:600.[5]

Over the past few decades newborn screening has been evolved into a system for screening of neonates for this disorder and potentially curative interventions prior to the onset of clinical symptoms can prevent the newborns sufferings from various abnormalities. Screening for CH is regularly performed in most developed countries and in some of the third world countries as well.[6] Data obtained from national and regional screening programs indicate that the incidence of congenital hypothyroidism varies globally. The incidence varies by geographic location and by ethnicity.[7-12]

Neonatal screening for the detection of CH implies two types of strategies: a primary TSH with backup T4 method and a primary T4 with backup TSH method. In addition, few screening programs use a combined primary TSH plus T4 approach. If the TSH is elevated, the T4 level also is tested. Specimen collection prior to 24 hours of age, prematurity and illness can affect the results of screening test and false positive or false negative results may occur.[13] Infants with elevated TSH and/or low T4require prompt follow-up and immediate clinical check-up and treatment under a pediatric endocrinologist.

The cost-benefit and effectiveness of health services play important roles and have implications in the design and evaluation of health policies. The high incidence and prevalence of metabolic diseases, particularly CH and the damage caused thereby, such as mental retardation should considered as a critical issue and health priority in

related policies in our country. In India national newborn screening program is still not being universally implemented, treatable cause of mental retardation like CH is being missed and cases are being diagnosed quite late.

Therefore, the objective of this study was to determine the incidence of CH in Neonates born in hospital based deliveries in our state and analyze the cost-effectiveness of the screening program to determine whether a new-born screening for CH is cost-beneficial from a societal perspective.

MATERIAL AND METHODS

Protocol of screening for Congenital Hypothyroidism

The study design was a cross-sectional screening study with cost-benefit analysis. Blood samples from neonates born at Department of Obstetrics & Gynaecology at Ram Manohar Lohia Combined Hospital, Lucknow India, were taken between 3 to 5 days after birth from heel prick. Family history of thyroid disease, history of thyroid disease or anti-thyroid medicine intake in mother along with other obstetric and relevant family history was recorded for each neonate. The study was approved by Institutional Ethics Committee and informed consent was taken from the parents of each neonate before enrollment for the study.

A total 1210 neonates whose parents were willing to participate in the study were enrolled and were subjected to screening test for Congenital Hypothyroidism. Our approach for screening the neonate was primary Thyroid Stimulating Hormone (TSH) test with supplemental T4 & TSH approach. A commercial third generation TSH assay was done using the Chemiluminescence assay method for screening of Congenital Hypothyroidism. Newborns with abnormal screening results (TSH>20mIU/L) were considered to suggest CH and additional follow-up testing of TSH and T4 was pursued within 2-3 weeks of age for diagnostic confirmation. Those neonates whose TSH values were still high and T4 was low, their parents were informed for the further evaluation by pediatric endocrinologist to confirm the status and start of treatment as soon as possible. Incidence was estimated, costs for the detection and treatment of abnormality were compared to the projected benefits of preventing the mental retardation and consequent productivity losses.

Cost effectiveness analysis of the screening of Congenital Hypothyroidism

To evaluate the cost effectiveness of screening, the cost of the screened group was calculated as the cost of testing which included actual cost of primary screening test (TSH estimation cost), second heel puncture and confirmatory test cost (backup T4 estimation within 2-3 weeks), cost of medical care in the first three years of life (includes cost of quarterly visit to a pediatric physician in government setup like ours and cost of medicine), periodic laboratory investigations and cost of medication till 70 years of the life as per statistics released by the Union ministry of health and family welfare which showed projected standard life expectancy in India at 67.3 years for males and 69.6 years for females (average 70 years) in 2011-15[14] and general and specialized physician visits up to end of life (Table I a). This was compared with the cost related to additional expenses occurred i.e. cost of periodic hospitalization, cost of medication for patients throughout the life, cost of special education and care of mentally retarded patients up to the end of life and loss of productivity for 30 years of his/her productive life, if child is not screened for congenital hypothyroidism, left untreated and develops irreversible cognitive motor impairment starting since birth till 70 years of his/her life (Table I b).

Costs for screening program consisting of hormone tests, diagnosis, medicine, treatments and physician charges were taken as in government organizations like our institute; training and education cost was calculated as per Inclusive education for disabled (IED) under Sarva Siksha Abhiyan (SSA) program of Central Government guidelines of Ministry of Human Resource Development (MHRD) of government of India for children with special needs (CWSN) which also includes children suffering from mental retardation.[15] Loss of productivity was calculated by per capita income of Uttar Pradesh[16] for 30 years of productive life.

RESULTS

Prevalence of Congenital Hypothyroidism: The demographic profile of neonates included in the study is shown in Table II. Out of 1210 neonates screened three were found positive for Congenital Hypothyroidism. Mother of two of these neonates was suffering from hypothyroidism and one was normal. Hypothyroid mothers had taken treatment as advised. The prevalence of Congenital Hypothyroidism in our study was 3/1,210 which is approximately one per 400 live births or 2.46/1000 live births.

With reference to Table I a, the cost per child with congenital hypothyroidism diagnosed in childhood due to the screening program which includes 1210 neonates (since in this study of 1210 neonates three cases were diagnosed) was calculated as Rs. 2, 49,100.The cost per child if the screening was not done and child was undiagnosed and not treated at right time which comes Rs. 21, 39,790 including all the variables (Table I b). These calculations shows that benefit to cost with regard to special education, care of mentally retarded patient and loss of productivity was approximately ten fold if the screening program for congenital hypothyroidism is included as a health policy and it also prevents mental retardation & growth complications of children suffering from CH.

Cost benefit of the CH screening was also quantitatively calculated by disability adjusted life years (DALYs) for our cohort of neonates. Disability-adjusted-life-years

(DALYs) is a common outcome metric for cost-effectiveness analyses, and the equations used for such calculations have been presented by Murray et al.[17] by the following formula-

DALY= YLL+YLD

Where: YLL: Years of Life Lost due to premature mortality.

YLD: Years Lived with Disability.

YLL = N x L [*where*: N= number of deaths; L = Standard life expectancy at age of death in years.

YLD = I x DW x L [*where:* I= number of incident cases; DW=disability weight; L= average duration of disability in years].

It measures the difference between a current situation and an ideal situation where everyone lives up to the age of standard life expectancy, and in perfect health.

In this study, we have ignored the lost years because of premature death (YLL) because CH is not resulted to mortality [N (0) × L (70)] therefore YLL was considered 0 (N=0). As YLL in this study is zero therefore, rate of index of DALY is equalled to the lost years of disability (YLD). If the child has been identified as CH patient through screening in first month of his/her life and treated timely, so the average standard of life expectancy in India (70 years) will be effective for the patients. Congenital hypothyroidism does not result in mortality, therefore DALY is actually the YLD for person living with congenital hypothyroidism or its consequences, which means that almost the entire life a child who was not been screened and treated timely for CH lives as disabled person.

For calculation of YLD the number of incident cases (I) was 2.46 (3 out of 1210neonates screened), standard life expectancy (L) was taken as 70 year according to statistics released by the Union ministry of health and family welfare in 2015, disability weight of mental retardation was the adapted from weight estimates reported in WHO's most recent update of GBD for 2004 and was equal to 0.459 for mental retardation.

DALY
= YLL =YLD
= 0+ (70 x 0.459 x 2.46)
= 0 + 79.04
= 79.04

The calculated DALY index was 79.04 in our study

(Note: The recent Global Burden of Disease (GBD) 2010 study published by IHME in December 2012 used an updated life expectancy standard for the calculation of YLL and based the YLD calculation on prevalence rather than incidence).

Table I a: Cost benefits variables if the screening is done and child is treated timely.

SN	Variables	Cost (Rs) /child	Total cost (Rs)
1.	Cost of screening for 1210 neonates (cost of TSH estimation)	120 x 1210/3	48,400
2.	Confirmatory test cost of three neonates screened positive for CH (second heal puncture and backup T4 estimation)	100 x 3	300
3.	Cost of medical care in the first 3 years of life (cost of quarterly visit to physician + medicine cost)	(500x4)+(3x4x110)	3,320
4.	Cost of medication from 4 to 70 years of life (cost of medicine @ 4 vials of thyroxin each year for next 67 years of life, per vial cost Rs.110 Which contains 100 tablets sufficient for three months)	(67x4x110)	29,480
5.	General and specialized physician visits up to the end of life (~500/visit, quarterly visit at least four times in a year)	500 x 4 x 67	1,34,000
6.	Cost of periodic laboratory tests (cost of quarterly TSH estimation)	4 x 120 x 70	33,600
Total cost (Rs.)			**2,49,100**

Table I b: Cost benefits variables if the screening is not done and child is undiagnosed and untreated at right time.

SN	Variables	Cost (Rs) /child	Total cost (Rs)
1.	Cost of periodic laboratory tests (cost of quarterly TSH estimation)	4 x 120 x 70	33,600
2.	Cost of periodic hospitalization (~ 10 days in a year)	10x1000	10,000
3.	Cost of special education of CWSN in appropriate environment till 18 years @ 3000/child/annum	3000x15	45,000
4.	Cost of care of mentally retarded patients up to the end of life (@1000/m)	12 x1000 x70	8,40,000
5.	Loss of productivity* (30 years of productive life)	40,373 x 30	12,11,190
Total cost (Rs.)			**21,39,790**

Table II: Demographic data of screened neonates.

S.N.	Variables	(N)
1.	**Gender**	
	Girls	570
	Boys	640
2.	**Age**	
	1-4 days	855
	5-7days	355
3.	**Primary TSH level**	
	0.04-3.99 mIU/L	944
	4-10 mIU/L	231
	10-20 mIU/L	29
	>20 mIU/L	**03**
	Test not possible due to inadequate sample	03

DISCUSSION

Congenital hypothyroidism can be defined as a lack of thyroid hormones present from birth. It may be due to defects in thyroid gland, pituitary gland or thyroid hormones themselves. The most common cause is failure of normal development of thyroid gland in about 75% of all cases of CH. Before birth thyroid gland is initially formed at the base of the brain, then moves down to its usual location below the larynx. When this normal development does not occur, the thyroid gland may be missing completely, the condition known as aplasia; or present partially in hypoplasia, or located at an abnormal site in ectopic thyroid. Other uncommon causes of congenital hypothyroidism are failure of the thyroid gland to make and release thyroid hormone (dyshormonogenesis) about 10% of all cases of CH and failure of the pituitary gland to stimulate the thyroid gland to make thyroid hormone (TSH deficiency in approximately 5% cases of CH.[6] Some infants develop a lack of thyroid hormones after birth. This is thought to represent primary hypothyroidism rather than CH. Children with untreated primary hypothyroidism do not experience the irreversible neurological problems that are seen with untreated CH. Congenital hypothyroidism results from congenital thyroid digenesis, defective hormone synthesis or severe iodine deficiency.

Congenital Hypothyroidism is a treatable disease and excellent outcome is possible if infants affected with CH get treated early. If the detection is delayed the prognosis for normal mental and neurologic performance is poor. It is reported that if disease can be detected within first two months of life and replacement therapy is begun soon after the detection, physical recovery is good and stature is normal.[18] Besides IQ greater than 85 in such infants, more than 70% of them may have some signs of minimal brain damage in their later life.[19]

With the emergence of newborn screening for inborn errors of metabolism in the 1960s, public health policies were developing regarding which conditions to include in screening and on what basis they should be chosen. The World Health Organization (WHO) took a leadership role in organizing international discussions on this issue. The first of the international discussions on newborn screening was in 1967, when a WHO Scientific Group on Screening for Inborn Errors of Metabolism was convened to consider the technical and ethical aspects of newborn screening including "whether and how newborn screening programmes could improve the health of mankind". The recommendations of that group of experts provide the general guidance used by most developing newborn screening programmes today (WHO Technical Report 1968).[20]

The prevalence and predominant disease etiology of CH, varies across different population groups around the world. With time newborn screening programs have proliferated and prevalence of CH has decreased with improved methods of detection and increased disease awareness in screened population. Globally, the prevalence of CH approaches 1:3000, with substantially higher prevalence in iodine deficient areas, sometimes in excess of 1:900.[21-24] Prevalence of CH may also vary with racial and ethnic differences across the populations. For example, in Japanese the prevalence is about 1:7600[25], while in Israel it is about three times higher. Variations in prevalence have also been reported within various populations. In the USA, for example, African-Americans appear to have CH prevalence about half that of Caucasians, while Hispanics have a rate about 40% higher and Native Americans may have an even higher rate. Studies in the UK[26] and South Africa[27] found that CH appears to be several times more prevalent in children of Asian (including Indian) ancestry; however, a recent study in India indicates a prevalence of approximately 1:2630 among people there. Studies have also found a higher prevalence (approximately 2:1) of CH among females. Recent research has shown that much of this discrepancy may be attributed to differences in thyroid ectopy and are gender related. Previous studies have reported a high incidence of CH in Iran.[28]

Cost effectiveness of screening programs for inherited disorders mainly depends on population frequencies. Initially Phenylketonuria (PKU) was the primary screened health disorders in the USA, Europe, Australia and New Zealand and its incidence was 1:15 000 in Caucasians. Simultaneous screening for CH was added which improved cost effectiveness due to fivefold high

(about 1:3500) incidence. In developed countries most of the newborn screening programmes were expanded during 1980's to include screening for CH and now newborn screening for CH has also became a priority in countries without large Caucasian populations. Since the incidence of CH is markedly increased in areas where the soil and food are poor in iodine, newborn screening for CH also began to emerge in developing countries, where iodine deficiency is a recognized problem. In line with these findings our study showed a very high prevalence of CH (3 out of 1210). The best way to detect infants with CH is by screening large populations of newborns. If the diagnosis is made and treatment started within a few weeks of birth, neurodevelopment outcome generally is normal and prevents mental retardation and growth complications. In our study we found DALY index was 79.04 which are much higher as compared to a finding of a national CH screening program in 2009-10 in Iran.[29]

Over half the babies born with congenital hypothyroidism look entirely normal and have no symptoms at all. The vast majority of children who have been screened at birth and diagnosed and treated from an early age will grow up normally. That is why it is so important that all children should be tested at birth. Congenital hypothyroidism can often be diagnosed before the baby shows any definite signs of the condition. Untreated, congenital hypothyroidism can result in impaired neurological development of the child. New born screening for congenital hypothyroidism has been included in neonatal screening programmes in the developed world.

It is a cause of concern that, in India despite the high reported incidence of CH, new-born screening is still not being implemented as a part of a defined screening policy. The purpose of this study was to further the cause and create awareness regarding significance of preventive testing to include CH screening in a nationwide universal screening program in India. Due to the safe motherhood intervention under the centrally-sponsored Janani Suraksha Yojana (JSY) scheme, institutional delivery of babies of poor women has increased. Because of incentives under JSY to give birth in a health facility, deliveries of a large segment of pregnant women in the rural areas of the country take place in government hospitals.

This scheme also provides performance based incentives to women health volunteers known as ASHA (Accredited Social Health Activist) for promoting institutional delivery among pregnant women which may also be utilized by state governments by linking for continuum for neonatal screening of CH. One such effort had been done last year in Kalahandi district by Sujata Dixit et al., where they have tried to make use of "Janani Suraksha Yojana" program run by the Indian government for identification of hot-spot areas for sickle cell disease using cord blood screening.[30]

The approach of conducting neonatal screening for CH in a government hospitals setup is feasible, appropriate and needs priority for the implementation of large-scale screening at point of delivery of neonates. The availability of qualified medical staff, and the quality of care that pregnant women are receiving through JSY scheme, can be utilized for collection and transportation of neonatal blood samples after 48 hour of birth in pre-existing health system.

The high incidence of hypothyroidism in a pilot study of 1210 neonates in UP strongly supports the implementation of a screening program for congenital hypothyroidism in all neonates born in our state. Early detection of Congenital Hypothyroidism by neonatal screening and its proper treatment in time will be beneficial in terms of saving affected child from mental retardation, improvement in quality of life and also it will be a major public health success in preventing numerous cases of intellectual lifetime disability and morbidity.

CONCLUSION

We recommend that routine screening programs for congenital hypothyroidism should be effective if performed within four to five days of birth with a heel prick blood test in a post-delivery hospital based settings. Neonates testing positive for hypothyroidism can be retested at one month to reconfirm the diagnosis and treatments can be commenced in good time to prevent clinical manifestations of CH.

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