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**PUBLISHED PAPER'S TITLE : PREVENTABLE MENTAL RETARDATION IN NEWBORNS: AN INDIAN PERSPECTIVE**

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*Research Paper*

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# PREVENTABLE MENTAL RETARDATION IN NEWBORNS: AN INDIAN PERSPECTIVE

**Rakesh Kumar Kalra[1], Manish Raj Kulshrestha[2], Piyush Bansal[3], Sumit Dokwal[2], Rupita Kulshrestha[4***]**

***Declaration***

The Declaration of the author for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) We Rakesh Kumar Kalra[1], Manish Raj Kulshrestha[2], Piyush Bansal[3], Sumit Dokwal[2], Rupita Kulshrestha[4]the authors of the research paper entitled Preventable Mental Retardation In Newborns: An Indian Perspective declare that ,we take the responsibility of the content and material of my paper as we ourself have written it and also have read the manuscript of our paper carefully. Also, we hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.we authorise the Editorial Board of the Journal to modify and edit the manuscript. we also give our consent to the publisher of ajmams to own the copyright of our research paper.

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**ABSTRACT:**

**BACKGROUND:** According to WHO, 4% of the population in India is mentally retarded, and 5 to 15% of sick newborns have a metabolic problem. Because of high birth rate, almost half a million infants with congenital malformation and/or inborn errors of metabolism are born every year in India and even an apparently healthy newborn has a significant risk of being maimed or killed by inborn error of metabolism. If detected early some of them are treatable or at least complications are preventable in many instances. Thus, mass screening is needed to prevent disability and death by early intervention, follow-up and counselling.

**METHODS:** The study was conducted in department of biochemistry and department of pediatrics, Christian Medical College and Hospital (CMCH), Ludhiana. All the newborns at CMCH from September 2008 to January 2010 were subjected to cord blood TSH estimation for congenital hypothyroidism (CH) and urine examination for aminoaciduria by thin layer chromatography (TLC).



**RESULT:** The observed incidence of congenital hypothyroidism and aminoaciduria among neonates born or admitted in Christian Medical College and Hospital, Ludhiana is 1:775 and 1:1550 respectively.

**DISCUSSION:** The actual incidence in the community may be higher as all deliveries are not being conducted in hospitals. Prevalence of CH seems to be higher in this part of globe than that suggested by earlier studies while prevalence of aminoaciduria in this part of India is different from that in western countries as well as southern India; Homocystinuria is the commonest aminoaciduria in this study population. However, larger multicentric screening programmes are required to find out the clear picture as well as to decrease/eliminate the burden of preventable mental retardation from the country.

**KEYWORDS: Aminoaciduria, Neonates, Incidence**

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**INTRODUCTION:**

World Health Organization estimates that 10% of the world's population has some form of mental disability and 1% suffers from severe incapacitating mental disorders.(1) Because of high birth rate, almost half a million infants with congenital malformation and/or inborn errors of metabolism are born every year in India and even an apparently healthy newborn has a significant risk of being maimed or killed by inborn error of metabolism. No nation-wide study is available in India. In addition, neither an incidence study nor a study on high risk group is available from Punjab.

Being a developing country, the health policies in India have typically targeted mortality and infectious morbidities but not disabilities. These policies have been successful in lowering infant mortality rates, but the net effect of these gains have been somewhat offset by an increase in disability.(2) Unfortunately, there is no place for congenital and inborn metabolic diseases because of their rarity and the cost for proper diagnosis.

If detected early some of them are treatable or at least complications are preventable e.g. phenylketonuria where early diagnosis and administration of phenylalanine restricted diet within first month of life can prevent complications like mental retardation.(3)

Clinical features of congenital hypothyroidism (CH) are often lacking at birth even up to first few weeks or month of life. Only up to 10% of affected infants are diagnosed clinically within the first month of life and 35% of infants with in the first 3 months of life. Since the development of first pilot screening program for detection of CH in Quebec in 1972; newborn screening have been introduced in USA, Canada, Western Europe, Israel, Japan, Australia and New Zealand. Studies have revealed that 78% of infants with CH treated before 3 months of life and none of infant treated after 6 month of life had an intelligence quotient of above 85.(4)

Congenital hypothyroidism (CH) is the most common cause of preventable Mental Retardation in children followed by phenylketonuria.(5) Thus, mass screening

is needed to prevent disability and death by early intervention, follow-up and counselling.(4)

Aminoaciduria is defined as increased amount of one or more amino acids in urine.(6) It can be diagnosed with bio-assay, chromatography, tandem mass spectrometry or HVE (High Voltage Electrophoresis). (7)

This study is designed keeping in view the high cost required to find out the prevalence of aminoaciduria. In this study thin layer chromatography (TLC) has been used to screen neonates as it is a reliable method for qualitative as well as semi quantitative estimation of amino acids in urine. In addition, it is cheaper and more readilyavailable than HPLC (High performance liquid chromatography) & TMS (Tandem mass spectrometry), while being better and faster than paper chromatography in estimation. For CH, cord blood TSH (CBTSH) estimation was done and only the cases with hyperthyrotropinemia were analyzed for $FT_3$,$FT_4$ and TSH at 72 hours of birth.

Both CH and aminoaciduria are justifiable for screening because:

1. High birth rate in India leading to a considerable burden of mentally retarded population.
2. These are the most common causes of preventable mental retardation in children.
3. To prevent mental retardation, diagnosis must be made early preferably within first few days life.
4. Clinical recognition is difficult(if not impossible) at birth and in early days of life.
5. Sensitive and specific screening tests are available.
6. Simple, cheap and effective treatment available if diagnosed early.
7. Cost benefit ratio is highly favorable.(4)

**MATERIALS & METHODS:**

The study was conducted in the Department of Biochemistry & Department of pediatrics, Christian Medical College and Hospital, Ludhiana, Punjab from September 2008 to January 2010. All the newborns born/ admitted in pediatric ward at this institution were subjected to screening for CH and aminoaciduria.

Parents/ guardians of the neonates were motivated to undergo the screening program and an informed consent was taken. A careful family history was taken for any of the inborn errors of metabolism in the form of history of mental retardation, frequent abortions, still-birth and early neonatal death.

In this prospective study, 2ml of blood sample was collected in a sterile container from umbilical cord at the time of birth from 1550 neonates who were born/admitted during study period. The sample was taken from the umbilical vessel by using 2cc disposable syringe. Samples were allowed to clot for 45 minutes. Serums were separated with centrifugation machine at 3000 rounds/minutes for 5-10 minutes.

Cord blood TSH were estimated by electrochemiluminescence immunoassay (ECLIA) on Elecsys 2010 immunoassay autoanalyzer with a diagnostic kit from Roche Diagnostics. Repeat thyroid function tests were also done with a reagent kit from Roche Diagnostics.

A repeat serum sample for determination of $FT_3$, $FT_4$ and TSH were done at 72 hours of life for neonates whose CBTSH were more than 20m IU/L. A detailed clinical examination was also conducted to look

for early signs of CH. Neonates with repeat TSH >20m IU/l were referred to pediatric endocrinologist for confirmation and early institution of therapy. The data obtained was tabulated and subjected to analysis using appropriate statistical tests.

Urine samples were collected from neonates. The prerequisite of the study was that the baby should have received at least 3-4 milk feeds before the sample was collected. (8)

Thin Layer Chromatography(TLC) was used as screening technique, using Butanol: Acetic Acid: Water as solvent (mobile phase) and Ninhydrin as staining agent. Plates precoated with cellulose were used for TLC. (8)

The urine was examined for cystine, ornithine, lysine, arginine, phenylalanine, tyrosine, threonine, homocystine, valine, isoleucine, leucine, methionine, glycine and hydroxyproline to screen following diseases:

Cystinuria, arginosuccinuria, phenylketonuria, alkaptonuria, threoninemia, homocystinuria, maple syrup urine disease, cystathionuria, glycinuria.

**RESULTS:**

The observed incidence of CH and aminoaciduria among neonates born or admitted in Christian Medical College and Hospital, Ludhiana is 1:775 (2:1550) and 1:1550 respectively; the only aminoaciduria found in this study group is homocystinuria.

The cut-off value of 20 mIU/L for cord blood TSH as screening tool, has shown poor sensitivity (as reported to be increased by perinatal stress) but 100% specificity.

**DISCUSSION:**

The actual incidence of CH and aminoaciduria in the community may be higher as all deliveries are not being conducted in hospitals. This may be a tip of iceberg phenomenon as certain communities have tradition of consanguineous marriages, have poor literacy and awareness; and still prefer home deliveries.

CH is the most common cause of preventable mental retardation in children**.** World wide incidence of CH has been reported from1:67 in Nigeria to 1:3398 in United Kingdom(9,10) while in Indian studies it has been 1:476 to 1:2804.(Table 1)(8,11-13) Incidence of CH is more in developing countries than in developed countries. The different prevalence rates of congenital hypothyroidism reported from different parts of world are suggested to be due to several factors such as the use of different T4/TSH levels as the tool for screening, established criteria for the diagnosis of CH being different among different studies, iodine deficiency, ethnic variations, environmental, genetics and familial factors.

In this study the incidence of amino acid disorder was found higher than that observed by Devi and Naushad (2004) at Hyderabad (India) where it was reported to be 1 per 3660(8). Other studies also suggest an incidence of 1:2500 (Karnataka) to 1:6250 (Australia).(Table 2)(14-15) Thus, the prevalence of aminoaciduria as detected in the present study may be taken as an alarm to conduct a larger neonatal screening programme, especially in absence of any

other study from this part of globe. According to previous studies, the incidence of aminoaciduria in India is found to be different from that in western countries where Phenylketonuria (PKU) was the commonest. In southern India also, the commonest disorders are phenylketonuria and tyrosinemia in Andhra Pradesh and Karnataka respectively.(Table 3)(8,15)

However, the data on the frequency of various metabolic disorders among subjects with mental retardation cannot be used to provide the frequency of these disorders at birth. Manjit Kaur and Verma in a study of 2560 symptomatic cases reported that the commonest amino acid disorders were homocystinuria, alkaptonuria, maple syrup urine disease (MSUD) and non-ketotic hyperglycinemia in north Indian population.(15) Interestingly, in a different study on clinical and biochemical studies in homocystinuria, the same authors mentioned that 10 out of 15 cases positive for homocystinuria were from Punjab. This study also indicates that homocystinuria is more common than phenylketonuria in north India.(16)

As the study was conducted on newborns, the relation with mental retardation could not be established. However, on follow up at the age of 6 months, the case identified with homocystinuria had development quotient of 0.5 for fine motor reflexes.

In a study done in Jordan, Hamamy et al found that approximately 30% of sporadic undiagnosed cases of mental retardation, congenital anomalies and dysmorphism may have an autosomal recessive etiology with risks of recurrence in future pregnancies.(17) The affected baby also had history of death of elder male sibling with respiratory cause (bronchopneumonia; as per record), at a private hospital at 10 months of age. Though bronchopneumonia is not related to homocystinuria, there is possibility of misdiagnosis or unrelated illness.

Kaur and Verma (1994) reported that all the 15 cases positive for homocystinuria had presented with some ophthalmic lesion. Though glaucoma was found in 2 (13.3%) out of 15 cases positive for homocystinuria.(15) In the present study also the case identified for homocystinuria had complaints of epiphora and glaucoma on follow up at 6 months of age. Thus, homocystinuria can lead to significant morbidities like delayed milestones and ophthalmic lesions if not treated in time.

A countrywide screening programme is required for CH and aminoaciduria detection to address this unmet need of the society, to further elaborate the incidence and to prevent high grade of significant morbidities associated with these disorders. IEC (information, education and communication) as well as genetic counselling should be in the reach of common people to increase the awareness about such preventable disorders and to facilitate their prevention, early diagnosis and appropriate timely management for the same.

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**TABLE 1**: The prevalence of CH in various Indian studies

| Hamamy HA, Masri AT, Al-Hadidy AM, Ajlouni KM. Consanguinity and genetic disorders. Profile from Jordan. Saudi Med J. 2007; 28(7):1015-7. **Study** | **Incidence** |
|---|---|
| Desai et al (1994) | 1:2804 |
| Devi et al (2004) | 1:1700 |
| Manglik et al (2004) | 1:600 |
| Ragupathy et al (2004) | 1:1344 |
| Sanghvi et al (2006) | 1:476 |
| Present study | 1:775 |

**TABLE 2:** The birth prevalence of aminoaciduria as reported worldwide in various studies

| **Region** | **Study** | **Birth Prevalence (aminoaciduria)** |
|---|---|---|
| British Columbia, Canada | Applegarth et al (2000) | 1/4000 |
| Australia | Wilken et al (2003) | 1/6250* |
| UK | Sanderon et al (2006) | 1/3750 |
| Karnataka | Appaji Rao (1991) | 1/2500** |
| Andhra Pradesh | Devi and Naushad (2004) | 1/ 3660 |
| Ludhiana | Present study | 1/1530 |

* excluding phenylketonuria ** excluding generalized aminoaciduria

**TABLE 3:** The commonest aminoaciduria detected in various regions

( PKU = Phenylketonuria; MSUD = Maple Syrup Urine Disease)

| REGION | MOST COMMON AMINOACIDURIA | STUDY |
|---|---|---|
| European countries (Belgium, Denmark, Germany, France, UK, Ireland, Netherlands, Switzerland) | PKU | Beckers et al (1973) |
| Japan | Histindinaemia | Naruse (1980) |
| Karnataka | Tyrosinaemia | Appaji Rao (1991) |
| Andhra Pradesh | PKU | Devi AR, Naushad SM (2004) |
| Ludhiana, Punjab | Homocystinuria | Present study |