Case Report

Congenital hypothyroidism : Importance of neonatal screening in preventing neurocognitive deficit

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Congenital hypothyroidism is one of the most common preventable causes of mental retardation in children. The prognosis of infants detected by neonatal screening and started on treatment early is excellent, with intelligence quotients similar to sibling or classmate without the disease. Department of ENT, Head and Neck Surgery, KVG Medical College, Sullia. A 15 year old boy came with history of head ache, generalized body ache and lack of concentration in school. He was a case of congenital hypothyroidism and was on irregular treatment for the last 13 years. The patient was advised strictly to continue the oral l-thyroxine 100µg one hour before food and come for regular follow-up. Definite intellectual deterioration is seen if oral l-thyroxine is not started within 50 days of life and the deterioration is irreversible. So in India newborn screening programs should be implemented as a national program as it is very important to diagnose and treat congenital hypothyroidism as soon as possible and to treat it effectively.

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Thyroid hormone plays a critical role in the development and maturation of the fetal brain[1]. Deficient production of thyroid hormone or a defect in thyroid hormone receptor activity can lead on to hypothyroidism[1]. Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation in children[1]. The incidence in India is estimated to be 2.1 per 1000 live births which is at least 8 times higher than what is reported in western literature[1].

CH was defined as TSH more than 20 mIU/L at less than 2 weeks of age or TSH more than 10mIU/L after 2 weeks of age[2]. Clinical features are not present at birth as some maternal thyroid hormone pass trans-placentally and is sufficient till the newborns thyroid starts functioning on its own[3]. Newborn screening programs should be confirmed by finding an elevated serum TSH and low T4 or free T4 level[3]. Other diagnostic tests, such as thyroid radionuclide uptake and scan, thyroid sonography, or serum thyroglobulin determination may help pinpoint the underlying etiology, although treatment should be started without these tests[3].

Oral levothyroxine being the drug of choice and the starting dose is 10 to 15 µg/kg/day[3]. The immediate goals of treatment are to rapidly raise the serum T4 above 130 nmol/L (10 ug/dL) and normalize serum TSH levels[3]. Frequent biochemical thyroid profiles monitoring in infancy is essential to ensure optimal neurocognitive outcome[3]. Serum TSH and free T4 should be measured every 1-2 months in the first 6 months of life and every 3-4 months thereafter[3]. In general, the prognosis of infants detected by screening and started on treatment early is excellent, with intelligence quotients similar to sibling or classmate without the disease[3].

Studies show that a lower neurocognitive outcome may occur in those infants started at a later age (>30 days of age), on lower l-thyroxine doses than currently recommended, and in those infants with more severe hypothyroidism[3].

Neonatal screening programs for detection of CH in neonatal period are widespread in the developed countries for the last three decades and are fast gaining momentum in India as well[4-9]. In most screening programs blood samples are collected at 5-6 days age, but with large number of babies being discharged early, cord blood samples are being used as well[9,10].

In India, it is very difficult to call back babies once discharged and an effective health system whereby babies who can be examined at home is practically impossible[9,10]. Thus cord blood remains a very practical alternative for screening purposes, and thus is the practice in some Asian countries[9,10]. The Indian Academy of Pediatrics recommends the use of cord blood samples for screening for congenital hypothyroidism[11].

Case Report

A 15 year old boy came with history of head ache and generalized bodyache and lack of concentration in school. He was examined in the department of ENT, KVG medical college and was found that he was a case of CH and was on irregular treatment for the last 13 years. Biochemical thyroid profile showed T3- 59ng/dl, T4 - 2.10 µg/dl and TSH -38.39 µIU/ml suggesting hypothyroid status. The patient had stopped taking elthroxin for the past 1 month causing a recurrence of the hypothyroid status.

Sonography of the neck showed both lobes were small in size with mild hypoechoic echotexture. The right lobe was 1.09x0.36x0.98 cm in dimension and the left lobe 0.8x 0.67x 0.96 cm in dimension. A benign lymph node measuring 5.7x2.7 mm was noted which had a fatty hilum on the left side at level[2].Major vessels of the neck were normal. The sonography concluded that the overall size of the thyroid was reduced with mild hypoechoic echotexture and benign cervical lymphadenopathy (Fig 1).

Presently the patient did not complain of decreased urine output or passing high colored urine but had constipation. The parents complained of poor school performance less in par with other children of his age. Slurred speech was present but no hoarseness was

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seen. Cold intolerance was present but no history of decreased activities and played well with other children.

Neonatal screening was not done in this patient and clinical diagnosis was missed in him till 2½ years. At the age of 2½ the parents took the baby to clinician with swelling of the face and abdomen of 1 week duration. The swelling and puffiness were uniform throughout his face not localized to the eyes and present only in morning hours. A uniform painless distension of the abdomen was seen of week duration. Reflexes were exaggerated but superficial and babinski reflexes were diminished. Clinical diagnosis of hypothyroidism was done and the investigations showed T3- 0.25ng/ml (0.75-2.4), T4- 0.96µg/dl (4.7-11.1), TSH- 51.90 µ IU/ml (0.2-5.0), serum cholesterol -566.0 mg/dl, Hb%- 9.0g/dl, blood urea- 35 mg/dl, serum creatinine – 1.8 mg/dl, total protein- 505 g/ml, serum albumin-2.5 gm/dl, serum globulin- 3.0 g/ml, TC -5000 cells/mm^3, DC-neutrophil-40%,eosinophil-2%, lymphocyte- 56%, basophil- 5%, monocytes- 2%.

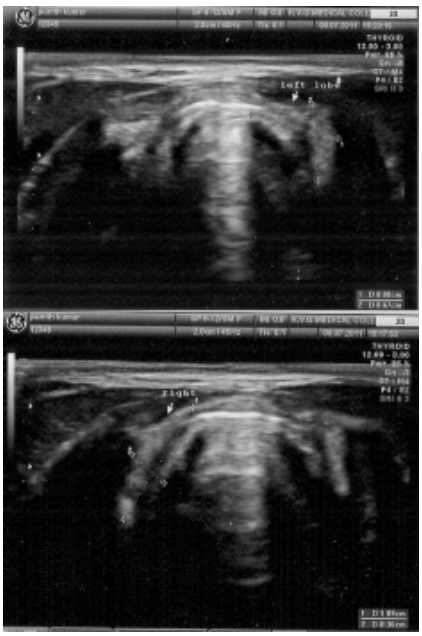

Fig 1 — Sonography of the right and left thyroid lobes showing short dimensions of the thyroid gland

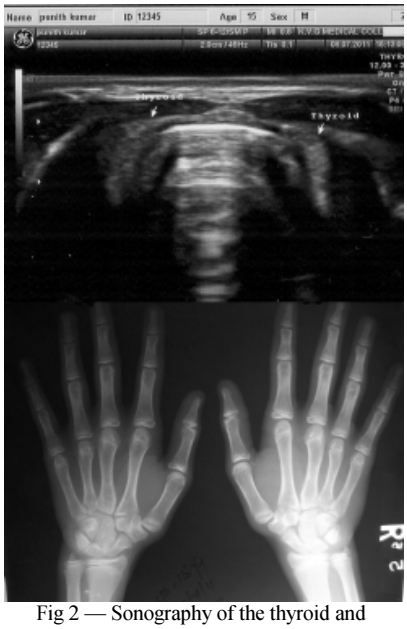

Fig 2 — Sonography of the thyroid and xray of the wrists

Peripheral blood smear showed normocytic hypochromic anemia. ECG showing low voltage complexes in all leads. Chest X-ray was within normal limits. X-rays of both the wrists joints showed delayed bone age corresponding to 5 years of age and the present X-ray wrists seems normal (Fig 2). His younger sister and brother were screened for hypothyroidism and found to be normal. In 100µg of elthroxin once orally in the morning one hour before food was started at 2½ years of age warning his parents not to stop the drug at any instance. The patient was advised initial 3 month follow up till 4 years and 6 months follow up till 10 years as literacy in family was low frequent follow were necessary. The patient had regular follow up till 6 years and later became irregular. He consulted with complains of relapse and later was advised to continue l-thyroxine. The patient is seen at 2½ years , 14 years and at 15 years (Fig 3).

Discussion

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth[3]. Thyroid hormone deficiency at birth is most commonly caused by a problem with thyroid gland development (dysgenesis) or a disorder of thyroid hormone biosynthesis (dyshormonogenesis)[3]. These disorders result in primary hypothyroidism[3].

Secondary or central hypothyroidism at birth results from a deficiency of thyroid stimulating hormone (TSH)[3]. Congenital hypothyroidism is classified into permanent and transient CH[3]. Permanent CH refers to a persistent deficiency of thyroid hormone that requires life-long treatment[3]. Transient CH refers to a temporary deficiency of thyroid hormone, discovered at birth, but then recovering to normal thyroid hormone production[3]. Recovery to euthyroidism typically occurs in the first few months or years of life[3].

Permanent CH can be further classified into permanent primary and secondary (or central) CH; transient primary CH has also been reported[3]. The underlying etiology of CH typically will determine whether hypothyroidism is permanent or transient, primary, secondary, or peripheral, and whether there is involvement of other organ systems[3]. Screening a newborn for congenital hypothyroidism is very important as mental retardation can be prevented in 85% of the cases with early initiation of thyroxine supplementation therapy before 3 months of age[12]. The incidence of the cases have risen from 1:7,000 to 1:10,000 to 1:3,000 to 1:4,000 after the introduction of worldwide newborn screening programs[13,14].

The incidence of congenital hypothyroidism in India varies from 1:2500 to 1:2800 live births[15]. Universal neonatal screening has been acknowledged as the most effective method to prevent the severe developmental and physical morbidities associated with congenital hypothyroidism[16]. However, despite proven benefits, efforts to implement it in India are still in its infancy[16]. CH features manifest minimally at birth making it difficult to diagnose on the basis of clinical features alone[16].

Clinical diagnosis is made in only 10% children in the first month of life and 30% in the first 3 months[17]. Hence there is a high risk of delayed diagnosis exposing the child to various degrees of developmental delay[17]. In view of the high incidence, apparently asymptomatic nature, propensity to cause neuro-developmental delay and residual impairment even with treatment, early detection and treatment of CH would be the most cost effective method to confront this problem[3]. Despite the crushing evidence of high inci-

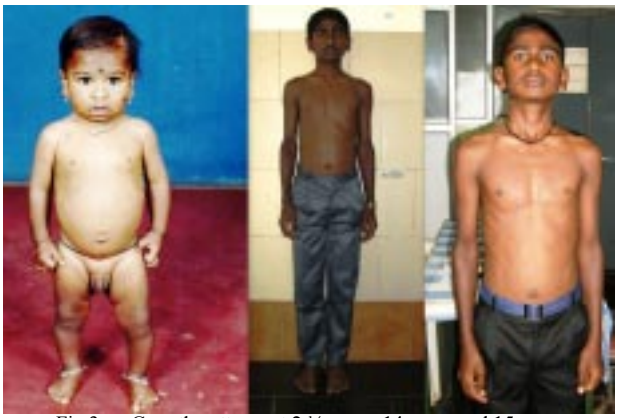

Fig 3 — Growth patterns at 2 ½ years, 14 years and 15 years

dence of CH, India continues to await a plausible universal screening program[3]. It is high time we start routine neonatal screening for CH to tackle this preventable cause of mental retardation[3].

As considerable difference in inheritance, prognosis and therapy are present, finding the etiology of the condition is important[18-20]. Thyroid dysgenesis (aplasia, ectopia, or hypoplasia) amounts to 80%, dyshormonogenesis amounts to 10-15%, pituitary or hypothalamic hypothyroidism, transient hypothyroidism and autoimmune mechanisms less than 5% of cases of CH[18-20]. Thyroid hormone replacement should be administered to all cases with biochemical confirmation of the diagnosis of hypothyroidism[12]. Even, cases of ectopic gland should be treated even if laboratory data reveal borderline or compensated hypothyroidism to prevent complications from enlargement of lingual or sublingual thyroid tissues[19]. Screening the newborn for presence or absence of functioning thyroid tissues is clinically important as functioning thyroid tissues have better neuropsychologic prognoses than those without[19,20].

CH due to enzyme defect in thyroxine production follow an autosomal recessive pattern of inheritance hence genetic counseling is required for patients wih this disorder[18-20]. CH could also result from transient abnormality in thyroid gland function, which subsequently recovers[21]. The possible explanations include iodine deficiency, transplacental passage of maternal TSH-binding inhibitory antibodies, and maternal exposure to radioiodine, iodine or antithyroid drugs[21].

Muir *et al*, in their 50 case study concluded that sonography cannot be an alternative to thyroid scintigraphy to define the cause of CH[20]. Takashima *et al*, suggested that thyroid scintigraphy is required only in patients with no visibility of the thyroid gland in the normal location and patients with an enlarged gland in the normal anatomic place with ultrasound[22]. Sonographic analysis has a potential to predict the prognosis of patients with suspected CH[22].

The condition is often subtle in presentation and many newborn infants remain undiagnosed at birth[23,24]. This is due to passage of maternal thyroid hormone across the placenta as it has protective effect on the fetal brain[25,26]. Even it is reported that the commonest form of CH has some moderately functioning thyroid tissue[25,26]. As the clinical features developed slowly and the need for early treatment has led to rampant newborn screening programs[25,26]. Only 35% world newborn population are screened and the major hit are the third world population, so clinicians here should recognize the disorder early[25,26].

On initial examination, the most common signs are umbilical hernia, macroglossia and cold or mottled skin[25,26]. Symptoms are not typical but maternal and pregnancy history is informative[25,26]. In 20% of cases gestation exceeds 42 weeks[25,26]. Hoarse cry, constipation, neonatal hyperbilirubinemia more than 3 weeks due to immaturity of hepatic glucuronyl transferase are common features seen[25,26].

Thyroid hormone is also important in the formation and maturation of bone[27,28]. Deficiency leads to a wide posterior fontanel of greater than 5 mm[27,28]. This, along with persistent jaundice and poor feeding are the most striking clinical features[27,28]. Common symptoms include decreased activity and increased sleep, feeding difficulty, constipation, and prolonged jaundice. On examination, common signs include myxedematous facies, large fontanels, macroglossia, a distended abdomen with umbilical hernia, and hypotonia[3]. Neurologic examination findings include hypotonia with delayed reflexes[23]. Skin may be cool to touch and mottled in appearance reflecting circulatory compromise[23]. X-rays can reveal absent femoral epiphyses in up to 54%[29].

CH appears to be associated with an increased risk of congenital malformations[30]. The prevalence of these extra thyroidal congenital malformations amount to 8.4%, cardiac malformations being more common[30]. Other associated malformations include spiky hair, cleft palate, neurologic abnormalities and genitourinary malformations[30]. Also, the incidence of congenital hypothyroidism is increased in patients with Down's Syndrome[31].

Conclusion

On detecting congenital hypothyroidism by neonatal thyroid screening programs treatment should be commenced within first month of life which makes prognosis for intellectual development better. Complete restoration of intellectual performance may not always be possible due to prenatal thyroxine deficiency.

Definite intellectual deterioration is seen if the treatment is not started within 50 days of life and the deterioration is irreversible. So in India newborn screening programs should be implemented as a national program as it is very important to diagnose and treat congenital hypothyroidism as soon as possible and to treat it effectively.

References

1 Sanghvi U, Diwakar KK — Universal newborn screening for congenital hypothyroidism. *Indian Pediatr* 2008; **45:** 331-2.
2 Martin CR — Thyroid disorders. In: Cloherty JP, Eichenwald EC, Stark AR, editors. Manual of Neonatal Care. 6th ed. Philadelphia: Lippincott, Williams and Wilkins; 2008. 19-27.
3 Maynika V Rastogi, Stephen H La Franchi — Congenital hypothyroidism: *Orphanet Journal of Rare Diseases* 2010, **5:** 17.
4 Newborn Screening for Congenital Hypothyroidism — Recommended Guidelines. *AAP Policy Statement. Pediatrics* 1993; **91:** 1203-9.
5 Dussault JH — The Anecdotal history of Screening for Congenital hypothyroidism. *J Clin Endocrinol & Metabolism* 1999; **84:** 4332-4.
6 Fagela-Domingo C, Padilla CD, Cutiongco EM — Screening for congenital hypothyroidism (CH) among Filipino newborn infants. Philippine Newborn Screening Study Group. *Southeast Asian J Trop Med Public Health* 1999; **30:** 20-2.
7 Feleke Y, Enquoselassie F, Deneke F, Abdulkadir J, Hawariat GW, Tilahun M, *et al* — Neonatal congenital hypothyroidism screening in Addis Ababa, Ethiopia. *East Afr Med J* 2000; **77:** 377-81.
8 Azizi F, Oladi B, Nafarabadi M, Hajipour R — Screening for congenital Hypothyroidism in Teheran; the effect of iodine deficiency on transient elevation of TSH in neonates. *J Facult Med SBUMS* 1993; **18:** 34-8.
9 Wu LL, Sazali BS, Adeeb N, Khalid BAK — Congenital hypothyroid screening using cord blood TSH. *Singapore Med J* 1999; **40:** 23-6.
10 Ordookhani A, Mirmiran P, Najafi R, Hedayati M, Azizi F — Congenital hypothyroidism in Iran. *Indian J Pediatr* 2003; **70:** 625-8.
11 Desai MP, Colaco MP, Ajgaokar AR, Mahadik CV, Rege C, Shirodkar VV, *et al* — Neonatal Screening for congenital hypothyroidism in a developing country: problems and strategies. *Indian J Pediatr* 1987; **54:** 571-81.
12 Dussault JH, Fisher DA — Hypothyroidism in infants and children. In: Braverman LE, Utiger RD, eds. The Thyroid. 6th ed. Philadelphia: JB Lippincott, 1991: 1219-36.
13 Alm J, Larsson A, Zetterstrom R — Congenital hypothyroidism in Sweden. Incidence and age at diagnosis. *Acta Paediatr Scand* 1978; **67:** 1-3.
14 Fisher DA — Second International Conference on Neonatal Thyroid Screening: progress report. *J Pediatr* 1983, **102:** 653-4.
15 Desai MP — The thyroid gland. In: Desai MP, Bhatia V, Menon PSN, editors. Pediatric Endocrine Disorders. 1st ed. New Delhi: Orient Longman; 2001. 183-202.

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16 Hulse JA, Grant DB, Clayton BE, Lilly P, Jackson D, Spracklan A, *et al* — Population screening for congenital hypothyroidism. *Br Med J* 1980; **280:** 675-8.

17 Price DA, Ehrlich RM, Walfish PG — Congenital hypothyroidism. Clinical and laboratory characteristics in infants detected by neonatal screening. *Arch Dis Child* 1981; **56:** 845-51.

18 Heyman S, Crigler JF, Treves S — Congenital hypothyroidism: 123I thyroidal uptake and scintigraphy. *J Pediatr* 1982; **101:** 571-4.

19 Wells RG, Duck SC — Technetium 99m pertechnetate thyroid scintigraphy: congenital hypothyroid screening. *Pediatr Radiol* 1986; **16:** 368-73.

20 Muir A, Daneman D, Daneman A, Ehrlich R — Thyroid scanning, ultrasound, and serum thyroglobulin in determining the origin of congenital hypothyroidism. *Am J Dis Child* 1988; **142:** 214-6.

21 Priya Nair, S Sobhakumar, lalitha Kailas — Diagnostic Re-evaluation of Children with Congenital Hypothyroidism. *Indian Pediatrics* 2010; **47:** 757-60.

22 Takashima S, Nomura N, Tanaka H, Itoh Y, Miki K, Harada T — Congenital Hypothyroidism: Assessment with Ultrasound: AJNR. *Am J Neuroradiol* 1995; **16:** 1117-23.

23 LaFranchi SH — Hypothyroidism. *Pediatr Clin North Am* 1979, **26:** 33-51.

24 Kaplan SA — Clinical pediatric endocrinology. Philadelphia: Saunders Solomon A Kaplan, 2 1990, 1990.

25 Vulsma T, Gons MH, de Vijlder JJ — Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989, **321:** 13-6.

26 Calvo R, Obregon MJ, de Ona Ruiz C, del Rey Escobar F, de Escobar Morreale G — Congenital hypothyroidism, as studied in rats. Crucial role of maternal thyroxine but not of 3,5,3'-triiodothyronine in the protection of the fetal brain. *J Clin Invest* 1990; **86:** 889-99.

27 Abu EO, Bord S, Horner A, Chatterjee VK, Compston JE — The expression of thyroid hormone receptors in human bone. *Bone* 1997; **21:** 137-42.

28 Murphy E, Williams GR — The thyroid and the skeleton. *Clin Endocrinol (Oxf)* 2004; **61:** 285-98.

29 Skordis N, Toumba M, Savva SC, Erakleous E, Topouzi M, Vogazianos M, Argyriou A — High prevalence of congenital hypothyroidism in the Greek Cypriot population: results of the neonatal screening program 1990- 2000. *J Pediatr Endocrinol* 2005; **18:** 453-61.

30 Olivieri A, Stazi MA, Mastroiacovo P, Fazzini C, Medda E, Spagnolo A — A population-based study on the frequency of additional congenital malformations in infants with congenital hypothyroidism:Italian Registry for Cong Hypothyroidism. *J Clin Endocrinol Metab* 2002; **87:** 557-62.

31 Kumar J, Gordillo R, Kaskel FJ, Druschel CM, Woroniecki RP — Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. *J Pediatr* 2009; **154:** 263-6.