Neurocognitive skills in children with congenital hypothyroidism attending the endocrine clinic of the Professorial Unit of the Lady Ridgeway Hospital for Children, Colombo

***Samanmali P Sumanasena[1], Nalika Gunawardena[2], Buddini Dissanayake[3], Supun Dilanka[3], Shamya de Silva[4]**

Sri Lanka Journal of Child Health, 2016; **45**(2):95-102

Abstract

Background: Early thyroxine replacement prevents intellectual impairment due to congenital hypothyroidism (CHT). There is minimal evidence on neurodevelopmental outcome of children commenced on thyroxine during early infancy from countries not screening for CHT.

Objective: To assess the neurocognitive skills of children with CHT of age group 6-10 years, attending the endocrine clinic of the Professorial Paediatric Unit, LRH compared to age matched controls and to assess the influence of age at diagnosis, initial thyroid stimulating hormone (TSH) levels, thyroxine commencement dose and number of clinic visits in the first year on neurocognitive skills.

Method: A retrospective study was carried out from 1st January 2010 to 1st January 2011 on children with CHT of age group 6-10 years, followed up in the endocrine clinic of the Professorial Paediatric Unit, LRH. Age matched healthy children aged 6-10 years were selected from similar socioeconomic backgrounds to compare the neurocognitive attainments. Neurocognitive skills were assessed using an age appropriate battery of instruments. Children older than 10 years were excluded as the assessment tools were designed only for the age range 6-10 years. Children with other co-morbidities adversely affecting their neurocognitive development were also excluded.

Results: Twenty three children with CHT of age group 6-10 years were followed up in the endocrine clinic of the Professorial Paediatric Unit, LRH during the study period and 2 were excluded. Forty two age matched controls of age group 6-10 years also participated in the study. The mean age of the children was 2.42±2.59 years. The mean TSH levels at diagnosis was 43.17± 34.25mU/L. Starting dose of thyroxine in the majority was less than 10µg/kg/day. Children with CHT performed less than their peers in all age ranges and in all areas of skills. Statistically significant differences were documented in the total performance percentiles at ages of 8 (p=0.0001) and 9 years (p=0.0002). Similarly, they performed less in literacy at 8 (p=0.015) and 9 years (p=0.004), verbal performance at 8 years (p= 0.0002) and numeracy in 9 years (p=0.035). There was no significant correlation between the neurocognitive scores and age at diagnosis, initial TSH levels, thyroxine commencement dose or the number of clinic visits in the first year.

Conclusions: Children with CHT of age group 6-10 years, attending the endocrine clinic of the Professorial Paediatric Unit, LRH had significantly reduced neurocognitive skills compared to age matched controls. There was no significant correlation between the neurocognitive scores and age at diagnosis, initial TSH levels, thyroxine commencement dose or number of clinic visits in the first year.

DOI: http://dx.doi.org/10.4038/sljch.v45i2.8095

(Key words: Congenital hypothyroidism, neurocognitive skills, school aged children)

[1]*Senior Lecturer in Disability Studies, Faculty of Medicine, University of Kelaniya, Ragama,* [2]*Senior Lecturer, Department of Community Medicine, Faculty of Medicine, University of Colombo,* [3]*Research Assistant,* [4]*Professor in Paediatrics, Department of Paediatrics, Faculty of Medicine, University of Colombo Sri Lanka*
**Correspondence: samanmalis@yahoo.com*

(Received on 8 August 2015: Accepted after revision on 18 September 2015)
The authors declare that there are no conflicts of interest
Personal funding was used for this project.

Introduction

Intellectual impairment due to congenital hypothyroidism (CHT) could be minimized by diagnosing and commencing treatment during the first 2 weeks of life[1,2]. Neonatal screening methods and management protocols to minimise the long term impact on the neurodevelopmental outcomes of these children are in place in several countries[1,2,3]. Sri Lanka has no national screening mechanism in place yet. However, in the Asian region Sri Lanka has excellent child health services with comparatively low infant and child mortality rates[4]. This health care system enables early clinical diagnosis of CHT during infancy and childhood.

CHT results from partial or total deficiency of thyroxine (T4) mainly due to thyroid dysgenesis or dyshormonogenesis[1,2]. Typically these children have low T4 levels and elevated thyroxine stimulating hormone (TSH) levels[1,2]. Thyroxine is essential for optimal growth and development of children starting from the intrauterine period and therefore if they are not diagnosed and treated during the early neonatal period, they may present with prolonged jaundice, constipation, noisy breathing, poor growth, heart failure or developmental delay[2]. The recommended commencement thyroxine dose is 10-15µg/kg/day[5]. Regular biochemical assays are recommended to confirm control.

Though the developed world initiated universal screening for CHT several decades ago, it is now evident that there is significant neurocognitive impairment in children with CHT in comparison to their peers and siblings, despite such early diagnosis and formal follow up procedures[6-13]. Specific deficits in neurocognitive functions are described in verbal competency, memory, reading comprehension, fine motor and visuospatial skills[6,7,12,13]. In most cohorts these changes impacted educational skills during the third year of formal education[7,12]. Some authors describe predictors of outcome for developmental attainments, such as dosage regimens, frequency of clinic reviews and socio economic background of child[6,7,9,14]. However, there is minimal data from developing countries without neonatal screening programmes about children with CHT who are diagnosed early in life based on their clinical features.

In Sri Lanka, most children are diagnosed on clinical symptoms and signs during infancy, subsequently confirmed by T4/TSH assays. Some children are confirmed to be hypothyroid only by elevated TSH values due to constraints in accessing laboratory facilities. Once diagnosed children are commenced on replacement therapy with L-thyroxine. These biochemical assays are not freely available throughout Sri Lanka, are relatively expensive and therefore not performed regularly. After diagnosis is confirmed most paediatricians rely on clinical assessments during follow up. However, regular growth and development surveillance is not practised within busy general paediatric clinics as they are time consuming. Hence patients face a double burden of delayed diagnosis and incomplete follow up. We undertook a study in children with CHT attending the endocrine clinic at the Lady Ridgeway Hospital (LRH), Colombo.

Objectives

- To assess the neurocognitive skills of children with CHT of age group 6-10 years, attending the endocrine clinic of the Professorial Paediatric Unit, LRH compared to age matched controls.

- To assess the influence of age at diagnosis, initial TSH levels, thyroxine commencement dose and number of clinic visits in the first year on neurocognitive skills.

Method

A retrospective study was carried out from 1st January 2010 to 1st January 2011 on children with CHT of age group 6-10 years, followed up in the endocrine clinic of the Professorial Paediatric Unit, LRH. The children were attending mainstream schools. Diagnosis was based on clinical features and confirmed with TSH only or thyroxine (T4) and TSH assays. Age matched healthy children aged 6-10 years were selected from similar socioeconomic backgrounds to compare the neuro-cognitive attainments. They were recruited randomly from two urban male and female schools. Compliance to treatment and clinic follow up were noted. Children older than 10 years were excluded from study as the instruments with which we assessed the children were designed only for the age range 6-10 years. Children with co-morbidities adversely affecting their neurocognitive development were excluded. All children were assessed within a learning

intervention clinic with a similar ambience to a class room.

An interviewer-based pretested questionnaire was used to collect data regarding diagnosis, treatment, follow up and socioeconomic background. The age at diagnosis, initial TSH levels, thyroxine commencement dose and number of clinic visits in the first year, were obtained from clinic records. A battery of instruments was developed to include essential skills required for satisfactory school performance in the age group 6-10 years. At present, Sri Lanka does not have any validated and standardized tools to assess school performance in children aged 6 to 10 years in Sinhala or Tamil languages. Activities to assess children aged 6, 7, 8, 9 and 10 years were designed according to the skills defined in the National Educational Skills Assessment Handbook, published by the National Institute of Education of Sri Lanka[15]. This lists standard skills to be achieved by a student for competent functioning within the class room at 7, 8, 9 and 10 years. Specific tasks pertaining to the areas of the study were identified by the principal investigator (PI). All assessments were carried out by the PI. Children were required to complete tasks within a defined time period. Raw scores were awarded for each item within the domains and percentile scores were calculated. Literacy, numeracy, verbal performance, visuo-spatial skills, sensory motor skills and short term memory were the six domains assessed using these tools (Table 1).

Data were analysed using Statistical Package for the Social Sciences (SPSS). The neuro cognitive skills attainment for each domain was compared between test and control groups for each age category, using box plots. The box illustrates the interquartile range (IQR), and the central horizontal line, the mean or median. Very low scores are represented by circles which are data points more than 1.5 IQR beyond the first or third quartile. The total neurodevelopmental scores attained per each group were compared using the t test.

Table 1: ***Domains assessed with detailed skills assessment in each age group***

Domain	6 years	7 and 8 years	9 and 10 years
Literacy	Pre reading (picture sequencing, pattern sequencing, picture differentiation), pre writing, letter identification, simple writing, comprehension	Reading, writing, comprehension (a paragraph from age specific national school text book not familiar to participant)	Reading, writing, comprehension, 1st and 2ndlanguage (a paragraph from age specific national school text book not familiar to participant)
Numeracy	Pre number skills (size concepts, sorting and patterns) number identification, coin identification	Arithmetic (simple additions and subtractions), geometry (3 D shape identification), algebra (bar graphs) (exercises derived from standard national text books not familiar to participant)	Arithmetic (divisions and multiplications), geometry (3 D shapes construction), algebra (bar graphs) (exercises derived from standard national text books not familiar to participant)
Verbal performance	Picture description, recites a rhyme	Picture description, recites poem	Picture description, recites a poem
Visuo-spatial skills	Shape identification Draw man	Picture discrimination, picture sequencing, left right orientation, draw house	Picture sequencing Reading the time
Sensory motor skills	throws a ball, tactile discrimination, pencil skills, knots	Colour sequencing, tactile discrimination, threading a shape, throws a ball	cutting, stitching, throws a ball
Memory	Recalls 3 digits	Recall 7 digits	Listens to an announcement and recalls items

Results

There were 23 children with CHT in the age group 6-10 years being followed up in the endocrine clinic of the Professorial Paediatric Unit, LRH during the study period. The parents of all 23 children gave their consent for the study. However, 2 children, one with Down syndrome and one with a history of neonatal meningitis were excluded from the study. Of the 21 children included in the study, 6 (28%) were male and 15 (72%) were female. There were 42 age matched healthy controls, aged 6-10 years selected from similar socioeconomic backgrounds. Of this 27 (64%) were male and 15 (36%) were female. Compliance to treatment and clinic follow up was one hundred percent in the study cohort.

The age distribution of cases and controls is shown in Figure 1.

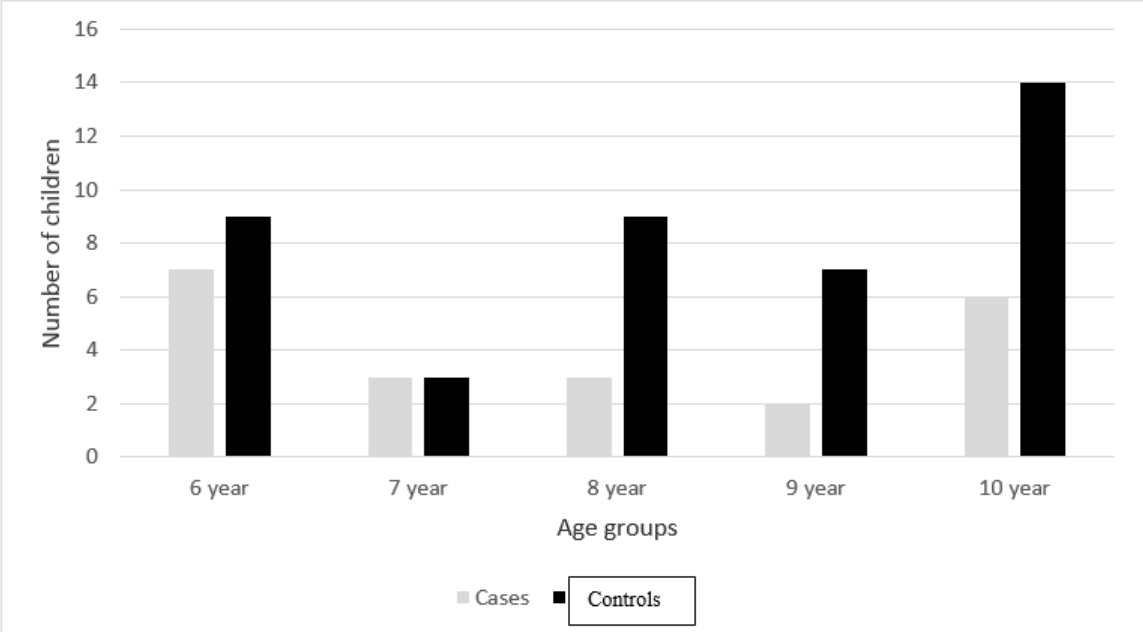

Figure 1: ***Age distribution of cases and controls***

Only 3 children in this cohort were diagnosed within the first month of life and 11 were diagnosed after the first year of life with a mean age at diagnosis of 2.42±2.59 years. T4 levels were assayed at diagnosis in only 16 children, but all children had a TSH assay as a confirmatory test. While one child had a TSH level above 100mU/l the majority had TSH levels ranging from 20-100mU/l at diagnosis with a mean TSH level of 43.17±34.25. Starting dose of thyroxine ranged from 5-10µg/kg/day with a mean of 6.20 ±4.62, with 17 commenced on a dose less than 10µg/kg/day, the recommended commencement dose. Maintenance dose of thyroxine was 6.82± 0.46µg/kg/day. Since T4 levels were not assayed routinely to monitor response to therapy it was not possible to calculate the time taken to normalise the T4 levels. All children visited the clinics 6-12 times during the first year of diagnosis but all of them did not undergo biochemical assays of the thyroid hormone profile.

Neuro-cognitive attainments

Children with CHT performed less than their peers in all age ranges and in all areas of skills i.e. literacy, numeracy, verbal performance, sensory motor, visuo-spatial and memory. Statistically significant differences were documented in the total performance percentiles in the age groups of 8 (p=0.0001) and 9 (p=0.0002) year old children (Figure 1).

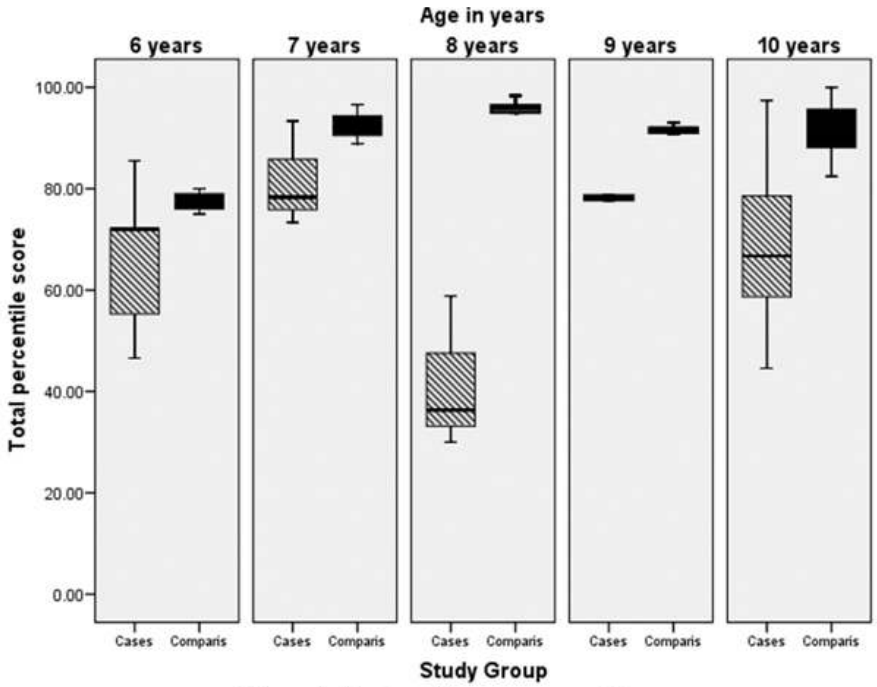

Figure 2: ***Total performance percentile scores***

Children with CHT had significantly lower scores in literacy at 8 (p= 0.015) and 9 years (p=0.004) compared to the controls (figure 3). Similarly the 8 year-old children in the test group had lower scores in verbal performance (p= 0.0002) and 9 year-olds performed less in numeracy (p= 0.035) in comparison to their healthy counterparts (figure 4 and 5).

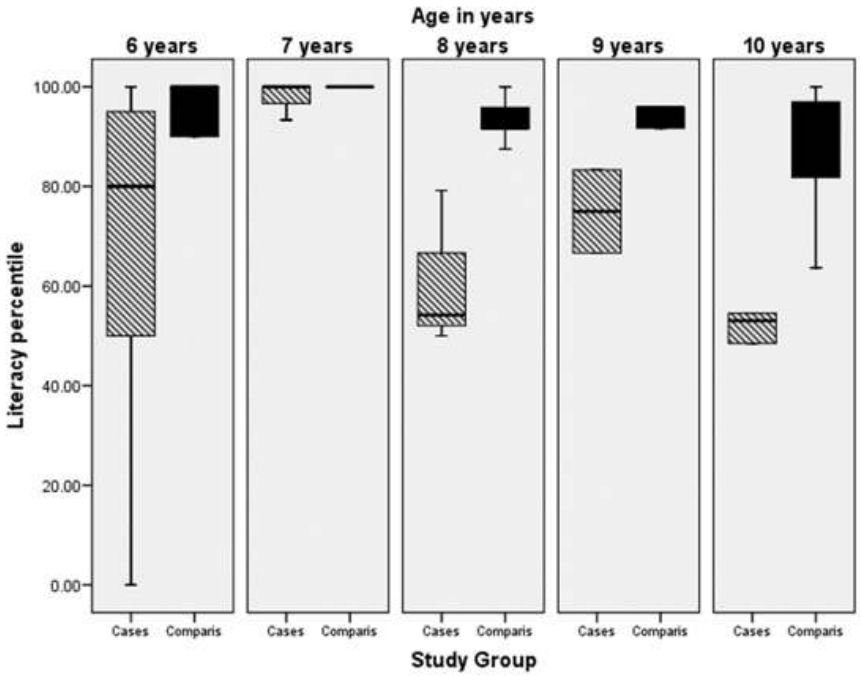

Figure 3: ***Literacy skills (Reading, writing, comprehension)***

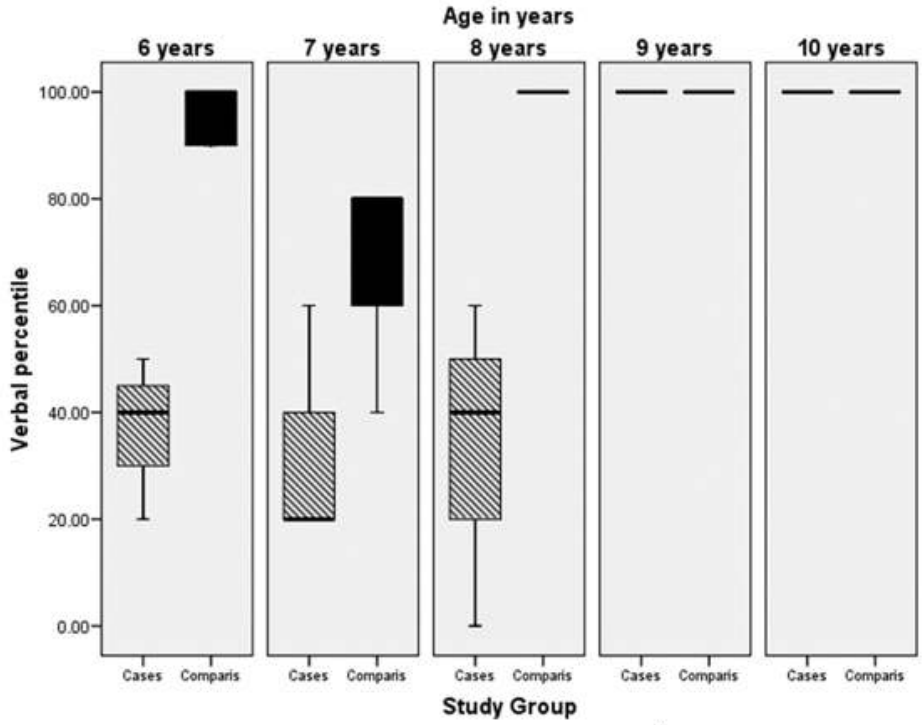

Figure 4: *Verbal performance skills percentile scores (recital, fluency, complexity)*

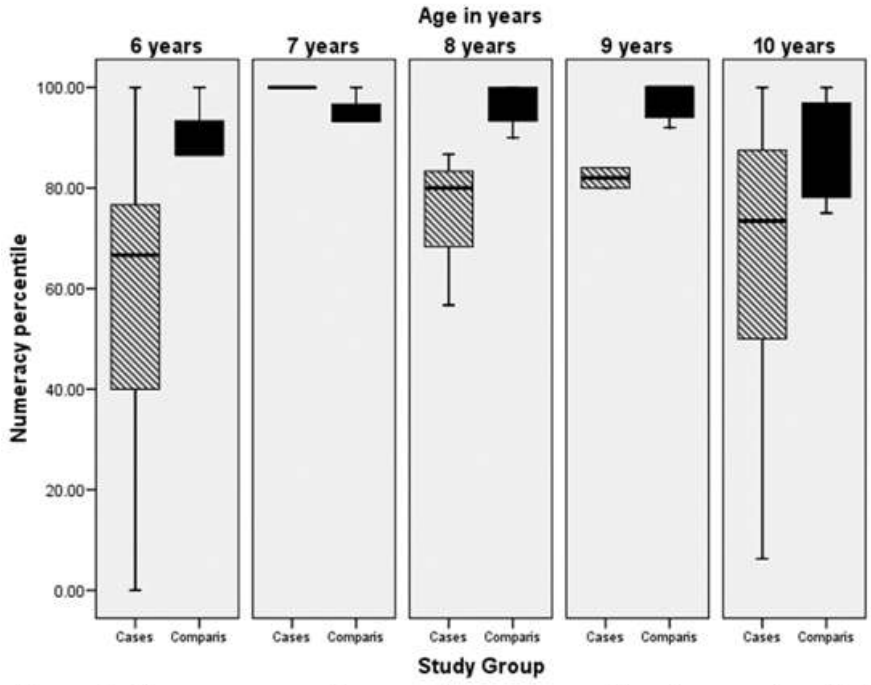

Figure 5: *Numeracy percentile scores (prenumber, arithmetic, geometry, algebra)*

We assessed the influence of age at diagnosis, initial TSH levels, thyroxine commencement dose and number of clinic visits in the first year on neurocognitive skills using multiple regression analysis. There was no significant association between the neurocognitive scores and the age at diagnosis, thyroxine commencement dose, initial TSH levels, and the number of clinic visits in the 1st year (Table 2).

Table 2
Influence of various factors on neurocognitive skills

Factors	B	P value
Age at diagnosis	-0.45	0.71
Initial TSH levels	0.91	0.35
Thyroxine commencement dose	0.46	0.73
No. of clinic visits in first year	0.45	0.71

Discussion

For many decades paediatricians have been aware of the requirement of thyroxine for early brain development. However, in most countries, programmes for neonatal screening are not in place. This study demonstrates that children with CHT show evidence of significant neurocognitive impairment across a spectrum of domains even if they are commenced on thyroxine during early infancy or childhood. Though medical science has advanced globally enabling early clinical detection of these infants, the impact on the developing brain remains significant emphasizing the need for biochemical screening prior to the onset of clinical signs. In several comparative studies conducted on children who were commenced on thyroxine following newborn screening, deficits in cognitive attainments are shown in similar domains and age groups. Though a significant difference is reflected in comparison to healthy peers, the deficits are minimal in studies conducted in developed countries. In contrast, children with CHT in our study showed a marked reduction in their skills in comparison to healthy peers. In our study the most statistically significant group of children who faced such difficulties belonged to the age group 8 and 9 years. This is keeping with the findings published by Koostra et al from Netherlands and Rovert from Canada where the facilities for screening were available[1,7]. The most probable reason for the stronger expression of difficulties during this specific age range is the transition from the early primary school (key stage1) to the year 3 and 4 (key stage 2) which requires complex skills to understand and perform the academic activities. Since these are essential skills to survive in the education system of Sri Lanka, it is very likely that these children will undergo multiple problems during classroom learning.

It is timely to introduce national neonatal screening for CHT in Sri Lanka and to incorporate stringent surveillance methods to detect development delay and introduce early intervention opportunities for these children in follow up clinics.

Though this is one of the few studies that describe the outcomes of delayed diagnosis of CHT in the region we could not access any standardised tools to assess the educational skills of these children. We attempted to minimise errors due to this deficit by using a comparative sample under strictly controlled circumstance.

Conclusions

- Children with CHT of age group 6-10 years, attending the endocrine clinic at LRH had significantly reduced neurocognitive skills compared to age matched controls.

- There was no relationship of neurocognitive skills to age at diagnosis, initial TSH levels, thyroxine commencement dose or number of clinic visits in the first year.

Acknowledgments

We acknowledge all participants of this study.

References

1. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. *Orphanet Journal of Rare Diseases* 2010; **5**: 10. http://dx.doi.org/10.1186/1750-1172-5-17
PMid: 20537182 PMCid: PMC2903524

2. Rose SR, Brown RS. Update of newborn screening and therapy for congenital hypothyroidism *Pediatrics* 2006; **117**: 2290. http://dx.doi.org/10.1542/peds.2006-0915
PMid: 16740880

3. Escobar GM, Escobar JO, delRey FE. Role of thyroid hormone during early brain development. The *European Journal of Endocrinology* 2004; **151**: U25-U37.

http://dx.doi.org/10.1542/peds.2006-0915
PMid: 16740880

4. Rannan-Eliya R, Sikurajapathy L. Sri Lanka: "Good practice" in expanding health care coverage. Colombo, Institute for Health Policy, 2008 (Research Studies Series No. 3).

5. Aronson R, Ehrlich RM, Bailey JD, Rovet JF. Growth in children with congenital hypothyroidism detected by neonatal screening. *Journal of Paediatrics* 1990; **116**:33-7. http://dx.doi.org/10.1016/S00223476(05)81641-5

6. Bargagna S, Dinetti D, Pinchera A, Marcheschi M, Montanelli L, Presciuttini S, Chivato L. School attainments in children with congenital hypothyroidism detected by neonatal screening and treated early in life; *European Journal of Endocrinology* 1999; **140**:407-13. http://dx.doi.org/10.1530/eje.0.1400407 PMid: 10229905

7. Kooistra L, Loane C, Vulsma T, Schellekens JMH, Meere JVD, Kalverbore AF. Motor and cognitive development in children with congenital hypothyroidism; a long tern evaluation of the effects of neonatal treatment. *Journal of Paediatrics* 1994; **124**(6): 903-9. http://dx.doi.org/10.1016/S00223476(05)83178-6

8. Komur M, Ozen S, Okuyaz C, Makharoblidze K, Erdogan S. Neurodevelopment evaluation in children with congenital hypothyroidism by Bayley-III. *Brain and Development* 2013; **35**(5) 392-7. http://dx.doi.org/10.1016/j.braindev.2012.07.003 PMid: 22858380

9. Kreisner E, Schermann L, Camargo-Neto E. Gross JL. Predictors of intellectual outcome in a cohort of Brazilian children with congenital hypothyroidism. *Clinical Endocrinology* 2004; **60**(2):250-5. http://dx.doi.org/10.1046/j.13652265.2004.01974.x PMid: 14725688

10. Oerback B, Sundet K, Kase BF, Heyerdahl S. Congenital hypothyroidism: Influence of disease severity and L-Thyroxine treatment on intellectual, motor and school-associated outcomes in young adults. *Pediatrics* 2003; **112**(4):923-30. http://dx.doi.org/10.1542/peds.112.4.923

11. Rovert JF. Long-term neuro-psychological sequelae of early-treated congenital hypothyroidism: Effects in adolescence. *Acta Paediatrica Suppl* 1999; **432**:88-95. http://dx.doi.org/10.1111/j.16512227.1999.tb01168.x

12. Rover JF. Children with congenital hypothyroidism and their siblings; do they really differ? *Pediatrics* 2005; **115**: 52-7.

13. Rovert JF, Ehrlich RM. Long-term effects of L-Thyroxine therapy for congenital hypothyroidism; *Journal of Paediatrics* 1995; **126**:380-6. http://dx.doi.org/10.1016/S00223476(95)70452-3

14. Dubuis JM, Glorieux J, Richer F, Deal CL, Dussault JH, Van Vliet G. Outcome of severe congenital hypothyroidism: Closing the developmental gap with early high dose levothyroxine treatment. *The Journal of Clinical Endocrinology & Metabolism* 1996; **81**(1): 222-7. http://dx.doi.org/10.1210/jcem.81.1.8550756

15. National Institute of Education. Essential educational skills for primary schools in key stage one and two. Primary and special education curriculum development section 1. 2002. National Institute of Education, Sri Lanka.