Original article

Neurodevelopmental outcome of congenital hypothyroidism in children between 1-5 years of age

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Abstract

Objective: To evaluate growth and development of children with congenital hypothyroidism (CHT) attending Pediatric Endocrine OPD BIRDEM. Methodology: It is a cross sectional study which was conducted at Pediatric outpatient department BIRDEM in a study period of 1 year (May 2008 to April 2009). A total number of 80 children with CHT were included in the study. A data sheet was used for each subject containing all the information. History and thorough physical examination was carried out including anthropometry , and developmental assessment. Developmental assessment was done according to Denver developmental screening test using standard charts of developmental progress which is appropriate for child's age.TSH and FT4 were done by chemiluminescent method in multichannel auto analyzer . Other investigations included bone x ray. ***Result:*** Total 80 children with congenital hypothyroidism between 1 to 5 years of age fulfilling the inclusion criteria were studied. Majority of the study population (71.20%) were diagnosed outside BIRDEM and 28.80% at BIRDEM. In the study population, 73.70% children were diagnosed within 1st three month of age and considered as early treated group, 26.20% diagnosed between three to nine month of age and classified as late treated group. Majority (56.20%) of the study population were female, and 43.70% were male child. All children among study sample were from non goiter endemic zone. Only 3 (5.0%) children among early treated group had maternal history of thyroid disorder and H/O ingestion of anti thyroid drugs and none among late treated group. 11(18.6%) early treated group and 2 (9.5%) late treated group children had affected peer with similar disorder and there was no family history of endocrine disorder among either group of study sample. Among 59 early treated group of children only 5(8.4%) had coarse facies, 2(3.3%) had protruded tongue and bradycardia, 4(6.7%) children had dry rough skin, 1(1.6%) was hypotonic, 2(3.3%) had delayed relaxation of ankle jerk and none had wide open fontanel. Out of 21 late treated group of children, 12(57.1%) had coarse facies, 4(19%) had protruded tongue, 6(28.5%) had bradycardia, 15(71.4%) children had dry rough skin, 16(76.1%) was hypotonic, 12(57.1%) had wide open fontanel and delayed relaxation of ankle jerk. Among 59 early treated group of children 53(89.8%), 51(86.4%), 55(93%) had normal and 6(10.1%), 8(13.5%), 4(6.7%) had delayed gross motor, fine motor and cognition respectively. Whereas among 21 late treated group 9(42%), 6(28.5%), 7(33.3%) had normal and 12(57%), 15(71.4%), 14(66.6%) children had delay in gross motor , fine motor and cognition respectively . There was no visual impairment among either group of children in study sample. Among 59 early treated group of children 57(96.6%) had normal hearing and 47(82.6%) had normal speech. Whereas among 21 late treated group, hearing impairment was seen among 7(25.9%) and speech delay was noticed among 16(76.1%) children. Among early treated group only 2% children had delayed radiological bone age, whereas 6% children among late treated group had delayed bone age. ***Conclusion:*** Congenital Hypothyroidism (CHT) is a serious condition of newborn babies, which leads to permanent mental and physical retardation if not identified within first few weeks of life. It is concluded that, the later the treatment is started the poorer the outcome will be.

Introduction

Congenital hypothyroidism (CHT) occurs when infants are unable to produce suf ficient amounts of thyroid hormone (thyroxine or T4), which is necessary for normal metabolism, growth and brain development.[1] Thyroid hormones play an essential role in brain development both during pre-and postnatal life. Unfortunately clinical symptoms are often late and nothing can be done at that point to save those children from permanent mental and physical handicapness. To identify the babies in early stage, screening of babies in first few days of life is the only choice.[2]

In the United states the incidence of CHT as detected through newborn screening is approximately 1 per 4000 births.[3] Data from most countries with well established newborn screening programs indicate an incidence of CHT of about 1 per 3000-40003, [4.]

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Some of the highest incidence (1 in 1400 to 1 in 2000) has been reported from various locations in the Middle East.[5]
Bangladesh is an iodine deficient area and thyroid related diseases are common in our country. The latest national survey shows that about 17% of the population is suffering from thyroid disorder. Incidence of congenital hypothyroidism in Bangladesh is not yet known.

Preliminary study shows an incidence of 1:2200, which is also much higher than world incidence (1:4000).[6] Most studies of CHT suggest a female to male ratio 2:1.[7]

Without prompt treatment, most af fected children gradually develop growth failure, irreversible mental retardation, and a variety of neuropsychological deficits. These complications have become rare since the introduction in the 1970s of routine neonatal screening and early treatment of CHT in developed countries[8], but the situation is dif ferent in Bangladesh.

Most cases of CHT present clinically during the first year of life.[9] Retrospective studies of patients with CHT have reported that delay of diagnosis and treatment beyond the first 1-3 months of life is likely to result in irreversible neuropsychological deficits. More recent prospective studies show that, screening neonate and treatment of affected infants within first week of life results, on average, in normal or near normal intellectual performance and growth at 5-12 years of age[10] . Both age at onset of therapy and quality of therapeutic control achieved during the first year of life af fect long term intellectual outcome.[11]

The present study is a cross sectional study in which growth parameters and neurodevelopmental status was assessed in children with CHT. The study population was divided into two groups on the basis of age of diagnosis and age of starting treatment into early and late treated group and comparison was done between these two groups of population to observe the relationship of neurodevelopmental status with time of initiation of treatment.

Method

It is a cross sectional study which was conducted at Pediatric outpatient department BIRDEM in a study period of 1 year (May 2008 to April 2009). A total number of 80 children with CHT were included in the study. Children with CHT diagnosed before one year of age, who are getting treatment with thyroxin and attending Pediatric Endocrine OPD BIRDEM between one to five years of age were included in the study. Some children were diagnosed at BIRDEM and others were diagnosed outside and were referred to BIRDEM Pediatric Endocrine OPD for further follow up.

Children who were diagnosed as congenital hypothyroidism after 1 year of age, who are getting treatment for less than six months and CHT associated with chromosomal disorder were excluded from the study.

There was no ethical concern for this study . Informed consent was obtained from the parents before including their children in the study . Structured questionnaire was used for data collection.

Collected data were analyzed with the help of SPSS version 12.0. Different variables were compared by unpaired t test. P value <0.05 was considered as significant.

Result

Total 80 children with congenital hypothyroidism between 1 to 5 years of age fulfilling the inclusion criteria were studied. Age, sex, mode of presentation and neurodevelopmental status were recorded. All the relevant findings were reviewed in the following tables and graphs.

In this cross sectional study , neurodevelopmental assessment was done among 80 children with congenital hypothyroidism between one to five years of age, diagnosed at or outside BIRDEM, attending Pediatric Endocrine OPD, BIRDEM, during the study period. Children diagnosed as CHT were on regular follow up visit at Pediatric Endocrine OPD, BIRDEM. In this study, neurodevelopmental assessment was done once among the study population during the study period (one year).

Among the study population, 23(28.8%) children were diagnosed at and 57(71.3%) diagnosed outside BIRDEM and were referred for further follow up. 35(43.7%) were male and 45(56.2%) were female children. 59(73.7%) were diagnosed within first three month of age who were categorized as early treated group, whereas 21(26.2%) diagnosed between three to nine month of age and were considered as late treated group. (Fig. ?, ??, III)

All children among study sample were from non-goiter endemic zone. Only 3 (5.0%) children among early treated group had maternal history of thyroid disorder and H/O ingestion of anti thyroid drugs and

none among late treated group. 1 1(18.6%) early treated group and 2 (9.5%) late treated group children had af fected peer with similar disorder and there was no family history of endocrine disorder among either group of study sample. (Table ?)

Among 59 early treated group of children only 5(8.4%) had coarse facies, 2(3.3%) had protruded tongue and bradycardia, 4(6.7%) children had dry rough skin, 1(1.6%) was hypotonic, 2(3.3%) had delayed relaxation of ankle jerk and none had wide-open fontanel. Out of 21 late treated group of children, 12(57.1%) had coarse facies, 4(19%) had protruded tongue, 6(28.5%) had bradycardia, 15(71.4%) children had dry rough skin, 16(76.1%) was hypotonic, 12(57.1%) had wide-open fontanel and delayed relaxation of ankle jerk (T able ? ?). These findings were consistent with similar study done in England by Glorleux J. et al. [12]

Among 59 early treated group of children 53(89.8%), 51(86.4%), 55(93%) had normal and 6(10.1%), 8(13.5%), 4(6.7%) had delayed gross motor, fine motor and cognition respectively . Whereas among 21 late treated group 9(42%), 6(28.5%), 7(33.3%) had normal and 12(57%), 15(71.4%), 14(66.6%) children had delay in gross motor, fine motor and cognition respectively. (Table ???). None of the children among early and late treated group had visual problem. (T able ?v). This study was consistent with a study by J A Hulse.37 In their study, children who had diagnostic delay beyond three month of age had significant gross and fine motor delay . In comparison regarding visual problem, 34(26.2%) children had squint, 2 had amblyopia and 3 had nystagmus that was unrelated to hypothyroidism.

Speech delay was present among 12(20%) early treated and 16(76%) late treated group of children. Hearing defect was present among 2(3.3%) early treated and 7(25%) late treated group of study sample. (Table v) This finding was consistent with the study by Robert JF . et al. [13] In their study they demonstrated language deficit and poor verbal skill among children who had diagnostic delay.

X- Ray for bone age was normal in 57(96.6%) and delayed in 2(3.4%) children among early treated group. Among late treated group normal bone age in 15(71.4%) and delayed in 6(28.5%) children.

Regarding thyroid function status, 57(96.6%) children had normal and 2(3.4%) had abnormal TSH, 54(91%) had normal and 5(8.4%) had abnormal FT4 value in early treated group. Among late treated group of study sample, 19(90.4%) had normal and 2(3.4%) had abnormal TSH, 18(85%) had normal and 3(14.2%) had abnormal FT4 value. In the current study, most of the study population among early and late treated group were biochemically euthyroid (Table v?), but significant growth and neurodevelopmental delay was seen among the late treated group of study sample. (Table II, III, IV)

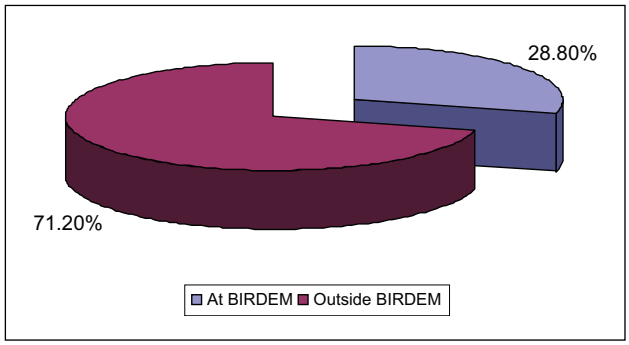

Fig.1: Pie diagram showing distribution of sample according to place of diagnosis

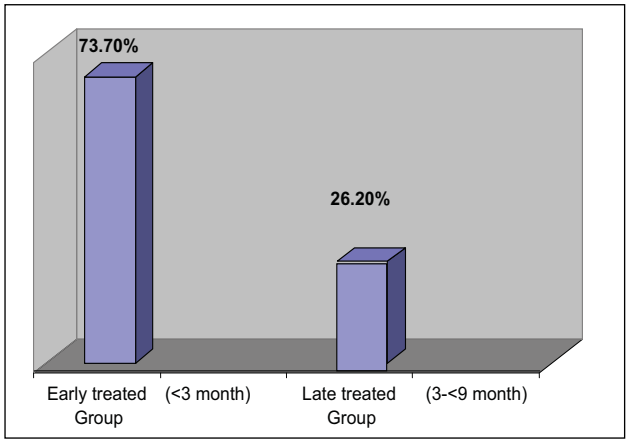

Fig.2: Bar diagram showing distribution of sample according to age of diagnosis

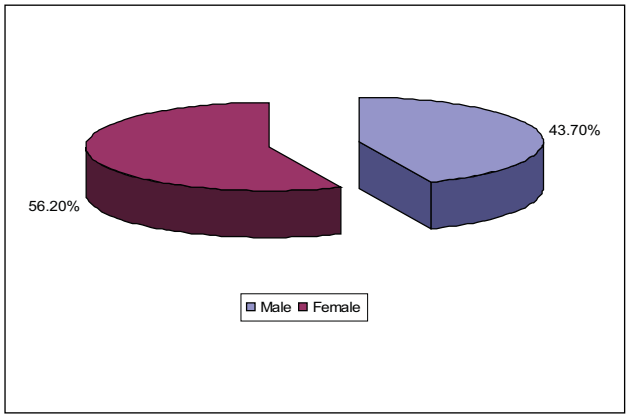

Fig.3: Pie diagram showing Distribution of sample According to sex

Majority (56.20%) of the study population was female, and 43.70% were male child.

Characteristics	Early treated group n(%)	Late treated group n(%)	*P* value
Maternal h/o thyroid disorder	**59**	**21**	
Present	3 (5.0)	0	0.331
Absent	56 (94.9)	21	
Maternal h/o ingestion of anti-thyroid drugs			
Yes	2 (3.3)	0	0.430
No	57 (96.6)	21	
Affected sib with similar disorder			
Present	11(18.6)	2(9.5)	0.054
Absent	48(81.3)	19(90.4)	
Family h/o of endocrine disorder			
Present	0	0	
Absent	59	21	

P value reached from unpaired t-test.

All children among study sample were from non goiter endemic zone. Only 3 (5.0%) children among early treated group had maternal history of thyroid disorder and H/O ingestion of anti thyroid drugs and none among late treated group which was not significant. 11(18.6%) early treated group and 2 (9.5%) late treated group children had af fected peer with similar disorder and there was no family history of endocrine disorder among either group of study sample.

Table II: Comparison on general examination findings among early and Late treated group during enrollment
P value reached from unpaired t-test.

Characteristics	Early treated group 59	Late treated group 21	P value
Appearance			
Normal	54(91.5)	9 (42.8)	.000
Coarse facies	5(8.4)	12 (57.1)	
Tongue			
Normal	57(96.6)	17(80.0)	.009
Protruded	2(3.3)	4(19.0)	
Pulse rate			
Normal	57(96.6)	15(71.4)	.000
Bradycardia	2(3.3)	6(28.5)	
Skin			
Normal	55(93.2)	6(28.5)	.000
Dry, rough	4(6.7)	15(71.4)	
Fontanel			
Normal	59(100)	9(42.8)	.000
Wide open	0	12(57.1)	
Muscle tone			
Normal	58(98.3)	5(23.8)	.000
Hypotonic	1(1.6)	16(76.1)	
Reflex			
Normal	57(96.6)	9(42.8)	.000
Delayed relaxation	2(3.3)	12(57.1)	

Among 59 early treated group of children only 5(8.4%) had coarse facies, 2(3.3%) had protruded tongue and bradycardia, 4(6.7%) children had dry rough skin, 1(1.6%) was hypotonic, 2(3.3%) had delayed relaxation of ankle jerk and none had wide-open fontanel. Out of 21 late treated group of children, 12(57.1%) had coarse facies, 4(19%) had protruded tongue, 6(28.5%) had bradycardia, 15(71.4%) children had dry rough skin, 16(76.1%) was hypotonic, 12(57.1%) had wide-open fontanel and delayed relaxation of ankle jerk

Among 59 early treated group of children 53(89.8%), 51(86.4%), 55(93%) had normal and 6(10.1%), 8(13.5%), 4(6.7%) had delayed gross motor, fine motor and cognition respectively . Whereas among 21 late treated group 9(42%), 6(28.5%), 7(33.3%) had normal and 12(57%), 15(71.4%), 14(66.6%) children had delay in gross motor, fine motor and cognition respectively.

Table III: Distribution of Neurodevelopmental status according to functional domains from Denver developmental screening test at the time of enrollment (gross & fine motor, cognition)

Domain	n (%)	P Value
Gross motor		
Early treated group	59	
Normal	53(89.8)	
Delayed	6(10.1)	
		.000
Late treated group	21	
Normal	9(42)	
Delayed	12(57)	
Fine motor		
Early treated group	59	
Normal	51(86.4)	
Delayed	8(13.5)	
		.000
Late treated group	21	
Normal	6(28.5)	
Delayed	15(71.4)	
Cognition		
Early treated group	59	
Normal	55(93.2)	
Impaired	4(6.7)	
		.000
Late treated group	21	
Normal	7(33.3)	
Impaired	14(66.6)	

P value reached from unpaired t-test.

Table IV: Neurodevelopmental status according to functional domains from Denver developmental screening test (vision, hearing, speech)

(n=80)

Domain	n (%)	P Value
Vision		
Early treated group	59	
Normal	59	
Abnormal	0	
Late treated group	21	
Normal	21	
Abnormal	0	
Hearing		
Early treated group	59	
Normal	57(96.6)	
Impaired	2(3.3)	
		.010
Late treated group	21	
Normal	14(66.60)	
Impaired	7(25.9)	
Speech		
Early treated group	59	
Normal	47(82.6)	
Delay	12(20.3)	
		.000
Late treated group	21	
Normal	5(23.8)	
Delay	16(76.1)	

P value reached from unpaired t-test.

There was no visual impairment among either group of children in study sample. Among 59 early treated group of children 57(96.6%) had normal hearing and 47(82.6%) had normal speech. Whereas among 21 late treated group, hearing impairment was seen among 7(25.9%) and speech delay was noticed among 16(76.1%) children. Comparison between two groups revealed speech delay was highly significant (P=.000) and hearing impairment was significant (P=.010).

Table V: Table showing X- ray bone age

	n (%)	P value
Early treated group	59	
Normal	57	
Delay	2	
		.000
Late treated group	21	
Normal	15	
Delay	6	

P value reached from unpaired t-test.

Table VI: Table showing serum TSH and FT4 level among early and Late treated group during enrollment

Early treated group (59)	TSH	FT4
Normal	57	54
Abnormal	2	5
Late treated group (21)		
Normal	19	18
Abnormal	2	3

Among early treated group of study sample, 57 had normal and 2 had abnormal TSH value, 54 had normal and 5 had abnormal FT4 value. Among late treated group 19 had normal and 2 had abnormal TSH, 18 had normal and 3 had abnormal FT4 value.
Normal TSH value: 0.7-5.7 µIU/ml
Normal FT4 value: 11.8-24.6 pmol/l

Discussion

In this cross sectional study , neurodevelopmental assessment was done among 80 children with congenital hypothyroidism between one to five years of age, diagnosed at or outside BIRDEM, attending Pediatric Endocrine OPD, BIRDEM, during the study period. Children diagnosed as CHT were on regular follow up visit at Pediatric Endocrine OPD, BIRDEM. In this study, neurodevelopmental assessment was done once among the study population during the study period (one year).

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Among 59 early treated group of children 53(89.8%), 51(86.4%), 55(93%) had normal and 6(10.1%), 8(13.5%), 4(6.7%) had delayed gross motor, fine motor and cognition respectively . Whereas among 21 late treated group 9(42%), 6(28.5%), 7(33.3%) had normal and 12(57%), 15(71.4%), 14(66.6%) children had delay in gross motor, fine motor and cognition respectively. (Table ???). None of the children among early and late treated group had visual problem. This study was consistent with a study by J A Hulse.14 In their study, children who had diagnostic delay beyond three month of age had significant gross and fine motor delay. In comparison regarding visual problem, 34(26.2%) children had squint, 2 had amblyopia and 3 had nystagmus that was unrelated to hypothyroidism.

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Regarding thyroid function status, 57(96.6%) children had normal and 2(3.4%) had abnormal TSH, 54(91%) had normal and 5(8.4%) had abnormal FT4 value in early treated group. Among late treated group of study sample, 19(90.4%) had normal and 2(3.4%) had abnormal TSH, 18(85%) had normal and 3(14.2%) had abnormal FT4 value. (Table v)

Newborn screening for CHT is one of the major achievements of medicine because early diagnosis and treatment has resulted in normal development in the vast majority of cases. Previous studies showed on outcome report of up to 10% of patients with residual problems regarding mental development and neurological symptoms despite early diagnosis.16 Factors clearly associated with a less favorable outcome in the current study are, late age of diagnosis and delay in commencement of treatment.

Conclusion

Congenital Hypothyroidism (CHT) is a serious condition of newborn babies, which leads to permanent mental and physical retardation if not identified

within first few weeks of life. There is an inverse relationship between age at diagnosis, commencement of treatment and neurodevelopmental outcome. In the present study , comparison between early and late treated group revealed that, children who were diagnosed at early age and started treatment early had favorable outcome in terms of growth and development in comparison to children with CHT who had delay in diagnosis and commencement of treatment. It is concluded that, the later the treatment is started the poorer the outcome will be.

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