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Congenital Hypothyroidism from Birth to One Year of Age Follow up: A Longitudinal Study

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Abstract

Background and objectives: Congenital hypothyroidism is the commonest neonatal endocrine disorder, and most common treatable causes of mental retardation. The study aimed to find out the important clinical presentations of congenital hypothyroidism at onset of diagnosis and their response to treatment over first year of life. **Methods:** A longitudinal study conducted in Rapareen Paediatric Hospital, from April, 1st 2015 to May, 1st 2018. The study enrolled 38 neonates and infants with congenital hypothyroidism who divided in two groups, according to the age of presentation. Those presented in the first four weeks of life, and those presented after four weeks of age. Clinical features documented and tests done for all cases in the form of T4 and thyroid stimulating hormone at presentation, and repeated each month for three months, then every three months for one year. Thyroxin started in standard doses of 10–15 mcg/kg/day once a day and titrated to keep T4 level in the normal upper range. Assessment of all growth parameters development was done at each visit. **Results:** Mean age of presentation was 27(±19) days. Clinical presentations were, large fontanel in 33(86.84%), feeding difficulties 32(84.21%), and large head 17(44.73%), prolonged neonatal jaundice 29(76.31%). All growth parameters showed improvement after three to six months of treatment in both groups, but there was a significant delay in social and language development in-group two. **Conclusions:** Early diagnosis and treatment is crucial, those received treatment in early life showed near normal growth and development.

Keywords: Congenital; Hypothyroidism; Neonates .

Introduction

Congenital hypothyroidism (CH) is an inadequate thyroid hormone production in newborn infants. In the majority of patients, CH caused by abnormal gland development (thyroid dysgenesis) that is a sporadic disorder and accounts for 85% of cases and the remaining 15% of cases are caused by defect in hormone synthesis, congenital hypothyroidism is the commonest neonatal endocrine disorder[1-3]. Congenital hypothyroidism is one of the commonest treatable causes of mental retardation. There is an inverse relationship between Intelligence Quotient (IQ) and the age at diagnosis[4,5]. Screening for congenital hypothyroidism recommended when the baby is three days of age or within seven days of birth, and before discharge. According to the American Academy of Paediatrics guidelines, any infant with a low T4 concentration and TSH concentration greater than 40 mU/L was considered to have primary hypothyroidism[6]. The clinical features of congenital hypothyroidism are often subtle and many newborns remain undiagnosed at birth6. Symptoms and signs included a hoarse cry, constipation, and neonatal hyperbilirubinemia for more than three weeks, decreased activity, large anterior fontanelle, poor feeding and weight gain, small stature or poor growth, constipation, and hypotonia. Congenital hypothyroidism is more common in infants with birth weights less than 2,000 g or more than 4,500 g[7,8]. Congenital hypothyroidism appears to be associated with an increased risk of congenital malformations[3,6]. The incidence of congenital hypothyroidism is increased in patients with Down›s Syndrome[9]. Even when diagnosed early, neurologic development may suffer if treatment is not optimized in the first two to three years of life[10]. The overall goal of therapy is ensuring that these patients are able to have growth and mental development. This is achieved by rapidly restoring serum free T4 and TSH to the normal range and then maintaining clinical and biochemical euthyroidism[10]. Levothyroxine is the treatment of choice; the recommended starting dose is 10 to 15 mcg/kg/day. The immediate goals of treatment are to rapidly raise the serum T4 above 130 nmol/L (10 ug/dL) and normalize serum TSH levels. Frequent laboratory monitoring in infancy

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is essential to ensure optimal neurocognitive outcome.

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. In general, the prognosis of infants detected by screening and started on treatment early is excellent, with IQs similar to sibling or classmate controls. 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 form of the disease[6].

Patients and Methods

This longitudinal study conducted in Rapareen Pediatric Teaching Hospital. The study was done in three years, starting from April 1st 2015 to May 1st 2018. The study enrolled 38 neonates (any baby under 28 days of age) and infants (any baby from birth to 12 months of age) presented with clinical features of congenital hypothyroidism. Two hundreds of healthy neonates and infants free any chronic problems taken as control. They had taken during their visiting the hospital for other reasons. The controls are taken to compare clinical and physical signs to patients with congenital hypothyroidism. Clinical features that alert the suspicion of congenital hypothyroidism were lethargy, slow movement, hoarse cry, feeding problems, poor feeding, constipation, poor linear growth, macroglossia, umbilical hernia, large fontanels (especially posterior) with wide cranial sutures, hypotonia, dry skin, hypothermia, distended abdomen, and prolonged jaundice[13]. Confirmatory tests done for all patients in the form of T4 and TSH levels at presentation, repeated each month for three months, then every three months for one year. Patients regarded to have congenital hypothyroid when acquiring both, the clinical features of congenital hypothyroidism and confirmatory high serum TSH and low T4 levels. Patients divided in two groups according to the age of presentation. Those presented within the first four weeks of age (Group One) and those presented after four weeks of age (Group Two).

Clinical features, growth parameters, motor and social developmental status comparison were done over one-year period and documented after three, six and twelve months. Medication in the form of thyroxin started on standard doses of 10–15 mcg/kg/day once a day and the dose titrated to keep serum T4 level in the upper normal. Comparison of clinical done for the cases (Group one) and control Group two). Growth parameters compared between both groups. Growth parameters followed over three months, six months, and one year after treatment. Patients with features of sepsis, mothers with history of hypothyroidism or on regular treatment of hypothyroidism, excluded from the study.

Gestational age determined from mother's menstrual history, and confirmed by modified Ballard's scoring (commonly used technique of gestational age assessment. It assigns a score to various criteria, the sum of all of which extrapolated to the gestational age of the fetus. These criteria divided into physical and neurological criteria. This scoring allows for the estimation of age in the range of 26 weeks-44 weeks)[12]. Preterm birth refers to a birth that occurs at or before 37 weeks of gestation, a term birth defined as a birth occurring between 37 and 42 weeks, and a post-term birth defined as a birth occurring after 42 weeks. Growth parameters are including weight, length and head circumference taken using infant scale for measuring weight, a tape measure for measuring length and head circumference. All growth parameters regarded normal when they lie between third and ninety-seventh percentile, while less than third percentile considered less than normal and more than ninety-seventh percentile considered above normal range. Motor and social delay concerned when less than seventy percent of expected for age and gender[13]. Data were analysed using the statistical package for social science (SPSS version 22). P-value of ≤ 0.05 considered as statistically significant. The ethical committee of College of Medicine of Hawler Medical University approved this study.

Results

Mean age of presentation at onset of diagnosis was 27(±19) days, males were 13(34.21%) cases, and male to female ratio was 1:1.9. Majority of patients were term neonates 34 (89.47%), while preterm deliveries observed in 3(7.89%) cases. History of the same condition was present in one patient (2.63%). Congenital heart disease was also observed in one patient as shown in Table 1.

Table (1): Socio-demographic data of the patients, No=38.

Characters	Variables	No. (%)(38)
Age of presentation in days (mean)	27 days (+_19)	
Gender	Male	13 (34.21%)
	Female	25 (65.79%)
Address	Urban	33 (86.85%)
	Rural	5 (13.15%)
Gestational age	Preterm	3 (7.89%)
	Term	34 (89.47%)
	Post term	1 (2.63%)
MOD	Normal vaginal delivery	17 (44.73%)
	Caesarean section	21(55.26%)
Family history	Positive	1(2.63%)
Dysmorphic facies	Present	1 (3.65%)
Associated Congenital heart diseases	Present	1 (2.63%)

Clinical presentations that observed at the onset of diagnosis were as follows: large head in 17(44.73%) patients, and 4(2%) found in control, with highly significant p-value of 0.0001. Large fontanel observed in 33(86.84%) patients, which was the most common observed value, compared to control 12(6%). Feeding difficulties observed in 32(84.21%) patients compared to 28(14%) in control with highly significant p-value of 0.001. Prolonged neonatal jaundice recorded in 29(76.31%) cases, while it was observed in 33(16.5%) neonates in control, with significant p-value of 0.001. The only non-significant feature was abdominal distension 18(47.36%) cases, while it was 78(38%) cases in control with p-value of 0.36. Other significant clinical presentations of significance are showed in Table 2.

Table (2): Clinical presentations found in cases and controls at first presentation, No=38.

Clinical presentations	Patients No. 38	Controls No. 200	p-value
Head size (large)	17 (44.73)	4(2%)	0.0001
Anterior fontanel	33(86.84%)	12(6%)	0.011
Posterior fontanel	28(73.68%)	8(4%)	0.0001
Feeding difficulties	32(84.21%)	28(14%)	0.001
Decreased activities	22(57.89%)	16(8%)	0.0008
Umbilical hernia	11(28.94%)	10(5%)	0.0004
Course facies	19(50%)	9(4.5%)	0.0001
Constipation	23(60.25%)	12(6%)	0.0003
Horse cry	21(55.26%)	14(7%)	0.0005
Abdominal distention	18(47.36%)	78 (39%)	0.36
Large tongue	24(63.15%)	3(1.5%)	0.0001
Lethargy and hypotonia	15(39.47%)	5(1.5%)	0.0001
Peripheral oedema	11(28.94%)	2(1.5%)	0.00003
Prolonged jaundice	29(76.31%)	33(15.5%)	0.001

Majority of the cases were presented and diagnosed in the first four weeks of life (group one). The majority of findings that observed were clearer in the second month of life (group two). Large head seen in 5(21.73%) of cases in group one, while 12(80%) of cases showed large head in the group two. Decreased activity was observed in 11(47.82%) of cases of group one, while it was 14(93.33%) in the group two, and the findings were highly significant p-value of 0.005 as shown in Table 3.

Table (3): Clinical presentations versus Onset of diagnosis.

Clinical presentations	Cases diagnosed at 1-4 weeks (Group one) No. of patients (23)	Cases diagnosed after 4 weeks (Group two) No. of patients (15)	p-value
Head size (large)	5(21.73%)	12(80%)	0.0003
Anterior fontanel (large)	15(65.21%)	13(86.66%)	0.27
Posterior fontanel (large)	18(76.26%)	9(60%)	0.28
Feeding difficulties	17(73.91%)	13((86.66%)	0.039
Decreased activities	11(47.82%)	14(93.33%)	0.005
Umbilical hernia	9(39.13%)	7((46.66%)	0.74
Course facies	7(30.43%)	13(86.66%)	0.002
Constipation	15(63.31%)	14(93.33%)	0.061
Abdominal distention	14(60.86%)	12(80%)	0.29
Large tongue	7(30.43%)	13(86.66%)	0.009
Lethargy and hypotonia	6(23.08%)	14(93.33%)	0.0001
Peripheral edema	5(21.73%)	10(66.66%)	0.008
Prolonged jaundice	19(82.6%)	13(86.66%)	0.9

The linear growth in form of weight, length and head circumference was compared in both groups. Weight was abnormal in 4(17.39%) patients in group one; while was abnormal in 9(60%) of patients in group two, with significant p-value of 0.043. Minority of cases in group one showed abnormal linear length 2(8.69%), and it was observed in 4(33.34%) in group two, p-value was not significant. The differences between head sizes of both groups were significant, as abnormal larger head circumference observed in 5(21.73%) patients in group one and 12(80%) in group two, with highly significant p-value shown in Table 4.

Table (4): Abnormal Linear growth at first presentation.

Characters	Patients diagnosed at 1-4 weeks (Group one) No. of patients 23(%)	Patients diagnosed after 4 weeks (Group two) No. of patients 15(%)	Total number of cases 38(%)	p-value
Weight	4(17.39)	9(60)	13 (34.21)	0.043
Length	2(8.69%)	4(33.34)	6(15.78)	0.16
Head circumference	5(21.73%)	12(80)	17(44.73)	0.0003

All growth parameters showed improvement after three months of standard therapy. The linear growth showed significant improvement in weight, and the abnormal weight decreased to 2(8.69%) cases in group one, while in group two it was decreased to 8(53.33%) cases, the findings were highly significant between two groups. The most important observed improvement was in head size.

Delayed motor development shown in 3(13%) cases in group one, 6(40%) patients in group two, the difference between two groups was statistically significant. While the difference in social development was more significant; group one showed normal development in all patients, while group two showed significant delay in social development. The p -value was markedly significant shown in Table 5.

Table (5): Abnormal linear growth and development at 3rd month of life follow up.

Characters	Cases diagnosed at 1-4 weeks (Group one) No. of patients (23)	Cases diagnosed after 4 weeks (Group two) No. of patients (15)	p-value
Weight	2(8.69)	8(53.33%)	0.001
Length	1(4.34%)	2(13.33%)	0.53
Head circumference	0(0%)	7(46.66%)	0.0005
Motor development	3(13%)	6(40%)	0.045
Social development	0(0%)	7(46.67%)	0.0002

All growth and developmental parameters showed remarkable improvement after six months of treatment in group one. The group two showed remarkable improvements in linear growth but showed delayed improvement in both social and language developments. No abnormal cases reported in group one, while 9(60%) of cases showed delay in group two, with p-value of <0.001 as shown in Table 6.

Table (6): Abnormal linear growth and development at 6-month age follow up.

Characters	Patients diagnosed at 1-4 weeks (Group one) No of patients (23)	Patients diagnosed after 4 weeks (Group two) No. of patients (15)	p-value
Weight	0(0%)	4 (26.66%)	0.0001
Length	1(4.34%)	1(6.66%)	0.034
Head circumference	0(0%)	5(33.33%)	0.0001
Motor development	1(4.34%)	3 (20%)	0.0009
Social development	0(0%)	9 (60%)	0.0001

After one year follow up, all parameters were within normal range in the group one patients, much better in the group two in all aspects of liner growth, while social and language developments clearly delayed in most of patients 12(80%) as shown in Table 7.

Table (7): Abnormal Linear growth at 12 months age follow up.

Characters	Patients diagnosed at 1-4 weeks (Group one) No of patients (23)	Patients diagnosed after 4 weeks (Group two) No. of patients (15)	p-value
Weight	0(0%)	1(6.66%)	0.0001
Length	1(4.34%)	1(6.66%)	0.034
Head circumference	0(0%)	3 (20%)	0.0001
Motor development	0(0%)	3 (20%)	0.0009
Social development	0(0%)	12 (80%)	0.0000

When liner growth observed over one year of age and compared, it showed improvement in all aspects; abnormal weight was seen in 13(34.21%) patients at the first presentation, while abnormal weight seen in 1(2.63%) patients at one year of age. Abnormal length was observed in 6(15.78%) patients in the first presentation while it was seen in 2(13.15%) patients at the end of first year. However, the least improvement growth parameter observed in head size.

Abnormal head size was seen in 17(44.73%) patients at the first presentation, while it seen in 3(7.89%) patients at one year of age, shown in Figure one

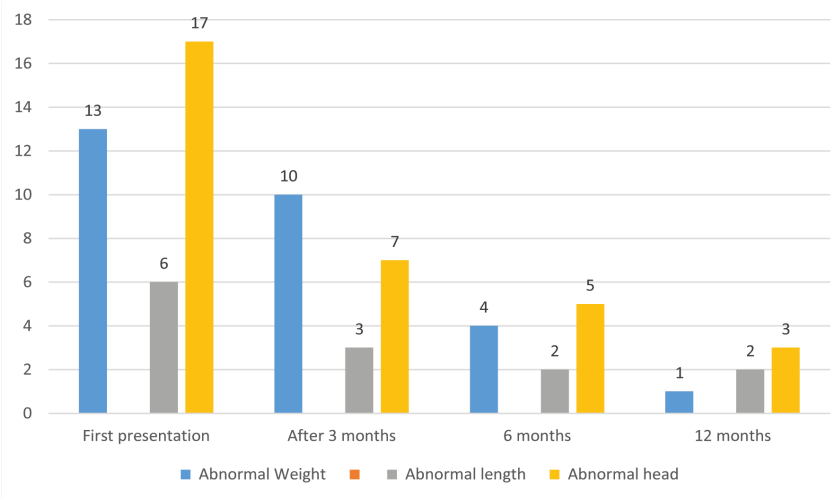

Figure (1): Abnormal anthropometric measures over one year follow up.

Motor development showed improvement over one-year period follow up. Motor development was abnormal in 9(23.68%) patients at three months of age, 4(10.52%) patients at six months of age and 3(7.89%) patients at one year of age. Social development showed more delay that is significant over one year follow up as shown in Figure 2.

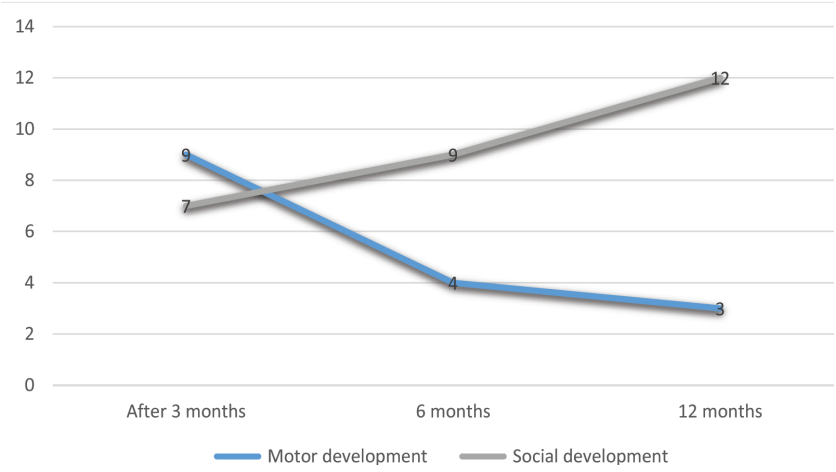

Figure (2): Abnormal motor and social development over one year follow up

Discussion

The study showed that most affected patients were females; male to female - ratio was 1:1.76, and the mean age of presentation was 27 days (±19), other sources showed that male to female ratio is 1:2 - 3[14].

The study showed that 34.21% of cases at first presentation were large for their age. Hypothyroid patients can be low birth weight or macrosomic[14]. The study showed that 2.63% of cases had associated congenital heart disease, while other studies found congenital heart disease to be 8.4%[15] probably because they have larger size study samples.

Congenital hypothyroidism has increased risk to be associated with Down syndrome, our study found 2.63% of cases of congenital hypothyroidism has down syndrome, this finding agree with Roberts HE et al [9], and Law WY et al 22 When they found the same associations. Clinical presentations found in our cases were feeding difficulty, large anterior fontanel, large posterior fontanel, and prolonged jaundice. The least common feature was umbilical hernia and peripheral edema, the findings agrees with other researchers[7,8] when they found most common features of congenital hypothyroidism were hoarse cry, constipation, neonatal jaundice, lethargy, and

poor feeding, this variety in the commonest presentation belongs probably to the onset of presentation and diagnosis in congenital hypothyroidsm[20].

The clinical features in our study were less prominent in cases that diagnosed at age less than four weeks (group one), and the features were more prominent in other cases that diagnosed after four weeks of age (group two). Studies concluded the same results, as most neonates with congenital hypothyroidism have few or no clinical features[21]. This is because some maternal T4 crosses placenta and umbilical cord. Serum T4 concentration is about 50% of normal infants[22].

The study found that most cases diagnosed at less than four weeks of age, have normal weight, height and head circumference, while those that diagnosed after four weeks of age has abnormal growth and development. These findings agree with Law WY et al[22]. They found that head circumference and weight increased in some cases at onset of early diagnosis. This is due to the fact that thyroid hormone is crucial for maturation and growth of bones and brain[23], they found also that congenital heart disease was associated with increased birth weight (48.5% of infants weighed greater than 3.5 kg) and an increased prevalence of non-thyroidal congenital abnormalities (8%) and congenital heart disease (3%).

Other researchers found that treatment of congenital hypothyroid before first month of age has excellent prognosis, and has normal maturation and growth [22, 23]. The findings in our study showed that some of early diagnosed cases has some delay in growth and development, as the researchers found that more severely affected infants, still may show slightly reduced growth and development despite proper diagnosis and treatment [21,22].

In cases with severe hypothyroidism, the likelihood of normal intellectual function is markedly reduced[9,23]. Other researchers also found that there is inverse relation between the onset of diagnosis and initiation of treatment, intelligent quotient, growth and development in later life[1,24]. Those findings rely with our study, when it found that growth of all parameters including weight, length and head circumference, social and motor development were abnormal and delayed, while those cases with congenital hypothyroidism who started treatment before one month of age, has better and near normal growth and development over long term follow up[3,23].

Conclusions

Early diagnosis and treatment is crucial, those received treatment in early life showed near normal growth and development, while those with delayed treatment had delay in growth, motor and social development.

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