Early Diagnosis and Specialist Care in the Management of Congenital Hypothyroidism

Sylvia Capistrano-Estrada,[1,2] Jacqueline O. Navarro,[3] Cynthia P. Cordero[4] and Carmencita David-Padilla[1,2]

[1.]Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines Manila
[2] Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila
[3]Department of Pediatrics, The Medical City
[4]Institute of Clinical Epidemiology – National Institutes of Health, University of the Philippines Manila

ABSTRACT

Background. Newborn screening for congenital hypothyroidism (CH) in the Philippines was introduced in 1996. It is universally accepted that early detection through newborn screening and timely treatment can improve the physical and neuro-cognitive development of patients. As of December 2010, the prevalence of CH is 1 in 3,324 among 2,389,959 newborns screened.

Objective. We sought to evaluate the role of timing of diagnosis, compliance with treatment, and specialist care on growth and development (mental and physical) of patients with congenital hypothyroidism detected through newborn screening.

Methods. Of the 326 patients identified through newborn screening between July 1996-December 2008 at the Newborn Screening Center–National Institutes of Health, 86 patients participated in the study. With the parents' or guardians' consent, general physical examination and neuro-cognitive evaluation were done; FT4 and TSH were determined. Prevalence of poor control of disease (high TSH with normal or low FT4 or normal TSH with low FT4), stunting, and cognitive delay were each estimated at 95% confidence level and the associations of early diagnosis, initial and continuing specialist care with these conditions were determined by multiple logistic regression analyses.

Results. The prevalences (95% confidence interval) were: poor control of disease 63% (52-73%), stunting 24% (15-34%) and neuro-developmental delay 17% (8-25%). Delay in one aspect of neuro-development was seen in 54% (43-66%). Early diagnosis was protective against poor control of disease (adjusted Odds Ratio, ORa= 0.24 [CI: 0.08-0.77]). Trends towards protection were seen for initial and continuing specialist care. For delay in at least one cognitive aspect, early diagnosis was found to be protective (ORa= 0.19 [CI 0.05-0.76]); results for specialist care were inconclusive. For stunting, low parent education was found to be a risk factor. (ORa of 5.45 [CI: 1.3-22.7]).

Conclusion. Fifty-four percent of the study patients had delay in one aspect of neuro-development. While other factors play a role in the outcome of CH, early diagnosis and treatment were shown to be protective of patients from poor control of disease and cognitive delays. Observed trends of positive benefits of specialist care at onset and continuing medical management, and the association of low parent education with poor growth should be considered in drafting specific guidelines for the long term follow-up care and monitoring of CH patients detected through newborn screening. The low percentage of participation and incomplete retrieval of information are major limitations of this retrospective study. This stresses the need for better monitoring tools that will ensure proper tracking, medical care and evaluation of CH patients.

Key Words: congenital hypothyroidism, compliance, neuro-cognitive development

Introduction

Congenital hypothyroidism (CH) is one of the more prevalent endocrine disorders in newborns affecting 1 in 3,000-4,000 newborns worldwide.[1,2,3] In the Philippines, the prevalence is 1:3,324 among 2,389,959 newborns screened.[4] Consistent with other studies, there is a 2:1 female to male incidence[2,5] and most cases are sporadic.[2] One consequence of untreated or unrecognized CH is mental deficiency. Newborn screening has been adopted by many countries in order to detect CH early and to institute adequate, early treatment so that mental and physical development can

Corresponding author: Sylvia B. Capistrano-Estrada, MD
Department of Pediatrics
College of Medicine and Philippine General Hospital
University of the Philippines Manila
625 Pedro Gil St. Ermita, Manila 1000 Philippines
Telephone: +632 3070780
Email: scestrada@post.upm.edu.ph

proceed normally in affected children. Factors that have been identified to affect long term intellectual outcome, motor development and/or physical growth include the severity of CH, pre-treatment T4 and TSH level, the initial dosage and timing of thyroxine replacement, socioeconomic status of the family and compliance to treatment.[3,6-17] In general, severe CH characterized by athyreosis, low pretreatment FT4, very high TSH, delayed neonatal bone aging, low initial thyroxine dosage and delayed initiation of treatment correlate with poor neurocognitive outcome and deviant infant growth. Treatment is generally aimed at achieving normal levels of FT4 within 2 weeks and of TSH within one month, and ensuring that these normalized levels are maintained, particularly for the first three years of life.[5] When these treatment goals are realized, CH is considered to be controlled. While there is consensus on the goals of CH treatment, the role of specialist-directed management in disease control has not been studied.

Although the introduction of systematic newborn screening for CH has eliminated severe cognitive and behavioral handicaps that occur with late diagnosis, it is well-recognized that even in early treated patients, some will show subnormal intelligence and subtle neurologic dysfunction.[8,10,11,18] Some reasons for these include severity of CH, inadequate thyroid hormone replacement due to poor compliance or lack of access to specialist directed care. Our study aimed to evaluate the roles of timing of diagnosis, compliance with treatment, and specialist care on disease control and growth and development (mental and physical) of patients with congenital hypothyroidism detected through newborn screening[16,18]

Methods

Recruitment of study participants

From March to November 2009, 135 families of 326 patients with confirmed CH listed in the newborn screening database of the Newborn Screening Center – National Institutes of Health (NSC-NIH), covering the period from July 1996 to Dec 2008, were successfully contacted and informed of the study. Only 87 participated.

Study procedures

Each study subject underwent a general physical examination by a licensed physician who was blinded as to the patients' CH etiology and current treatment. Their length (children 2 years old or younger) or height (children older than 2 years old), and corresponding standardized scores (Z-scores), using World Health Organization (WHO) growth charts, were recorded.[19,20] Patients with Z-scores of -2 and below were classified as stunted.

A comprehensive psychometric evaluation was conducted on all the patients. Evaluators were blinded as to the patients' CH etiology and current treatment. Participants 35 months and younger were evaluated by a developmental pediatrician who determined their developmental quotient (DQ) through a neurodevelopmental evaluation, psychosocial behavior assessment, and Griffiths Mental Developmental Scales-Extended Revised. A developmental psychologist evaluated the full scale intelligence quotient (FSIQ) of patients who were older than 35 months. Children 36 to 70 months old were evaluated using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI); while the Wechsler Intelligence Scale for Children (WISC) was used for subjects 71 months and older.

During the study visit, the parents or guardians were requested to complete a questionnaire on socio-demographic data, family history and therapeutic regimen of the patient. Three milliliters (3 ml) of venous blood was collected from each child and assayed for thyrotropin (thyroid stimulating hormone; TSH) and free thyroxine (FT4). Assays were performed at the Manila Endocrine Laboratory. Poor control of CH was defined as elevated TSH with low or normal FT4 or normal TSH with low FT4 based on the normal reference range set by the laboratory.

The primary physician or endocrinologist of each child was requested to complete a questionnaire describing the child's general health status, laboratory tests results, family medical history and medical management (date and initial dose of L-thyroxine, compliance). Questionnaires were hand carried or sent by courier to the physicians and retrieved by the study nurse.

Methods of Data Analysis.

The prevalence of poor control of disease (CH) (based on the thyroid hormone profile obtained during the study visit), stunted height (based on WHO Z-scores) and cognitive delay (deficiency in any one aspect of IQ or DQ) were estimated at the 95% confidence level. The associations of early treatment, initial and continuing specialist care with these characteristics were determined using multiple logistic regression analysis. Patients with no information on early treatment were considered as having late treatment. Likewise, no information on specialist care was considered as absence of specialist care. Age at the time of assessment, gender, parent's educational attainment and initial TSH were included in the analysis as confounders. Control of disease was included as a potential factor for stunting and cognitive delay.

Ethical Considerations

This research protocol was reviewed and approved by the technical and ethics review boards of the National Institutes of Health. Written informed consents were obtained from the parents or guardians of the participants.

Results

A total of 326 patients with confirmed CH are listed in the newborn screening database of the NSC-NIH, covering the period July 1996 to Dec 2008. All were contacted but of these, 123 (38%) could not be reached because the listed phone numbers were not in use, 61 (19%) had no contact information, and 7 (2%) had died (reasons unknown). Of the 135 parents who could be contacted, 19 consented but were unable to come for the study visit due to work, and 29 refused to participate. A total of 87 CH patients, through their parents or guardians, consented to be part of the study. Of these, one patient with Down Syndrome was excluded. The percentage of total cases participating in the study was 26% (86/325).

Demographic characteristics of study sample

There were 54 females and 32 male study participants. The mean age at assessment was 36.2 months. The youngest patient was 4 months and the oldest was 103 months (8.5 years). Seventy-five (87%) had at least one parent with a college education or higher; 52% reported an annual family income of PhP100,000 or more.

Treatment details.

Patients were started on L-thyroxine (4-15 mcg/kg/day, n=31) between 9 to 224 days after birth with a mean of 37 days and a median of 26 days. Sixty-four percent were treated less than 30 days from birth with a mean of 20 days. Initial TSH ranged from 7.26 to 5968.8 IU/ml with a median of 96.6.

Data on the number of days for pretreatment TSH to reach normal range was available only in 62 patients. Further, there was a wide variation in the timing and number of post treatment TSH determinations among the study patients. The shortest time was 23 days and the longest was 1598 days (4.4 years). The median is 128 days. Table 1 shows other treatment details.

Prevalence of Poor Biochemical Control of CH, Stunting and Cognitive Delay

Table 2 shows that 62.8% had poor biochemical control at the time of assessment; 24% were stunted; 16.6% had low scores for IQ or DQ and 54.4% were assessed to be deficient in one aspect of IQ or DQ.

Relationship of early diagnosis, treatment and specialist care with CH outcome.

Early diagnosis (and treatment) was found to have a protective association against poor control of disease when statistical adjustments were made for age at assessment, gender and parents' education. Including initial TSH level as

Table 1. Patients' baseline and treatment details

Treatment Parameters	Median	Range
Age L-thyroxine started, days, n=80	26.0	9 – 224
TSH (before treatment) IU/ml, n=79	96.6	7.26 -5968.8
Days to reach normal TSH, n=62	128.0	23 - 1598
	Number	Percent
Timing of Treatment		
Early ≤30 days from birth, mean=20.1, SD 5.8, 9-30	55	64.0
Late > 30 days from birth, mean 74.1, SD 60.9, 32-224	25	29.0
No Information	6	7.0
Specialist Care at Diagnosis		
Yes	58	67.4
No	17	19.8
No Information	11	12.8
Continuing Specialist Care		
Yes	60	69.8
Lost	15	17.4
No Information	11	12.8

Table 2. Frequency of Poor Control of CH, Stunting and Cognitive Delay

Condition of Interest	Number of children evaluated	Number with condition	Frequency, Percent (95% Confidence Interval)
Poor Control of CH	86	54	62.8 (52.4 - 73.2)
Stunting	86	21	24.0 (15.0 - 34.0)
Cognitive Delay*			
Low FSIQ or DQ	79	13	16.5 (8.1 - 24.8)
Delay in one aspect of FSIQ or DQ	79	43	54.4 (43.2 –65.7)

*7 did not have information
FSIQ: Full Scale Intelligence Quotient
DQ: Developmental Quotient

a control variable yielded similar but imprecise results. Crude analysis showed trends of protection associated with specialist care (initial and continuing management) but the effect of these trends were inconclusive in the adjusted or controlled analysis (Table 3).

Table 3 also illustrates that parents' low education (high school or less) was a risk factor for stunting. The contributions of early diagnosis and treatment, initial and continuing specialist care to stunting were inconclusive.

When statistical adjustments were made for age at assessment, gender, parents' education, control of the disease and initial TSH, early diagnosis was found to have a protective association against delay in any one aspect (i.e. verbal IQ, performance IQ, processing speed quotient or perceptual reasoning, working memory index) of cognition. The contributions of specialist care on at least one aspect of cognitive delay were inconclusive (Table 4). For overall cognitive delay, results were inconclusive (Table 4).

Table 3. Crude and adjusted Odds Ratios for the outcomes poor control of disease and stunting

Factor of Interest	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Poor Control of Disease		
≤ 30 days, diagnosis and treatment	0.20 (0.05 – 0.64)	0.24 (0.08- 0.77)
Specialist, Initial	0.34 (0.10 -1.03)	0.51 (0.16 – 1.62)
Specialist, Continuing	0.29 (0.08 -0.95)	0.45 (0.13 -1.51)
Age at assessment, months	0.82 (-10.31 to 11.95)**	1.00 (0.98-1.02)
Male Gender	0.79 (0.30 – 2.16)	0.64 (0.23 -1.76)
High school or less (Parents' Education)	1.68 (0.36 – 10.57)	1.61 (0.35 -7.36)
Stunting		
≤ 30 days, diagnosis and treatment	1.17 (0.38 – 3.92)	1.12 (0.30-4.12)
Specialist, Initial	0.55 (0.18 -1.76)	0.37 (0.11 –1.30)
Specialist, Continuing	1.11 (0.34 -4.02)	1.65 (0.43 -6.36)
Age at assessment, months	11.73 (-.53 to 24.00) **	0.97 (0.95-1.00)
Male Gender	0.80 (0.24 – 2.49)	0.66 (0.21-2.06)
High school or less (Parent's Education)	4.80 (1.04 – 22.37)	5.45 (1.31 -22.73)
Poor Control of Disease	0.73 (0.24 -2.29)	0.57 (0.17 -1.92)

*Including initial TSH in the analysis yielded similar results. For poor control of disease adj OR of early diagnosis and treatment is 0.31 95% CI (0.09-1.00)

** Difference between the means of the patients with the condition and those without (95% CI)

Table 4. Crude and adjusted Odds Ratios for cognitive delay

Factor of Interest	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Delay in any one aspect		
≤ 30 days diagnosis and treatment	0.53 (0.18 – 1.52)	0.19 (0.05-0.76)
Specialist, Initial	1.30 (0.46 -3.71)	0.70 (0.19 – 2.58)
Specialist, Continuing	1.64 (0.56 -4.84)	1.44 (0.38 -5.47)
Age at assessment, months	14.24 (3.72 – 24.76)**	1.03(1.004-1.06)
Male Gender	0.38 (0.13 – 1.09)	0.39 (0.12-1.31)
High school or less (Parent's Education)	3.30 (0.57 – 34.31)	3.63 (0.62 -21.1)
TSH, initial	278.66 (-97.29-654.60)**	1.004 (1.0002-1.01)
Poor Control of Disease	1.68 (0.36 -10.57)	0.65 (0.20 -2.16)
Overall cognitive delay (low FSIQ or DQ)		
≤ 30 days diagnosis and treatment	0.86 (0.22 – 3.73)	0.91 (0.21-3.88)
Specialist, Initial	1.12 (0.27 -5.56)	1.14 (0.23 –5.53)
Specialist, Continuing	0.98 (0.24 -4.87)	0.92 (0.19 - 4.33)
Age at assessment, months	11.30 (-3.26 to 25.86)**	1.01 (0.99- 1.04)
Male Gender	0.49 (0.08 – 2.18)	0.72 (0.16-3.12)
High school or less (Parent's Education)	0.60 (0.01 – 5.32)	0.67 (0.07- 6.24)
TSH, initial	233.55 (404.65-871.75)**	1.0002(0.999-1.0008)
Poor Control of Disease	0.98 (0.25 -4.23)	1.00 (0.25-4.01)

*n=73 patients

**Difference between the means of the patients with and without the condition (95% CI)

Discussion

Cognitive delays and stunting are preventable consequences of CH. While newborn screening has made a significant contribution to the prevention of these undesirable consequences, reports about their continued occurrence remain.[12,21] Good control of CH is central to good physical growth and neurocognitive parameters. It is now recognized that other factors aside from early detection are associated with favorable long term outcomes. Our study's main objective was to assess whether timing of diagnosis, treatment and specialist care promoted good control of the hypothyroidism and minimized stunting and cognitive delays.

We found that 64% of the participants studied were prescribed thyroid hormone replacement in varying doses (4-15 mcg/kg/day) before 30 days of age. Early treatment with high dose L-thyroxine (10-15 mcg/kg/day) has been shown to result in a more rapid decline of TSH and normal values of T4 signifying control of CH.[8,11] However, the benefit of this regimen is still debatable as it has resulted in subtle problems of attention and behavior.[11] In our study, we were able to obtain the duration for TSH to normalize only in 62 patients. The median duration for TSH to normalize was 128 days. There were 2 patients (Patients 50 and 67) whose TSH normalized between 1233-1598 days; and 4 (Patients 23, 37, 51, 82) whose TSHs normalized between 667-933 days. TSH is a parameter used to titrate dosage of L-thyroxine along with physical growth. A highly elevated blood TSH with low T4 suggests poor control of hypothyroidism hence, the AAP recommendation of high dose thyroid hormone replacement within 2 weeks of birth among patients with CH and subsequent monitoring to ensure good biochemical blood levels.[5] Patient 37 is a female infant who had hormone replacement at 11 days, had clinic visits every 4-6 months with specialist until the age of 5 years and then was lost to follow-up. Patient 51 is a male infant who was treated late (204 days), did not have benefit of specialist care at the onset, and was non-compliant with clinic visits due to the distance between his residence and clinic of specialist. Patient 82 is a female infant who was treated early on day 20 of life, had good follow up for the first 5 years and was lost to follow-up thereafter. For these 3 patients, non-compliance can explain the persistently elevated TSH. How about patients 23, 50 and 67, all treated early between 20-22 days, compliant but with persistently elevated TSH for long duration? What can explain this? Kara and co–workers report that 5.4% of 500 CH patients have persistently elevated TSH inspite of adequate treatment. In the same cohort, the TSH in 9 patients did not normalize during the observation period. The delay was not related to etiology of CH or the pretreatment T4 and TSH values.[22] This observation is worth elucidating in another prospective research.

We also found that 63% of the study participants were in poor biochemical control at the time of their neurodevelopmental assessment. This suggests that other factors such as compliance with treatment were involved in control of the disease. We also found that early diagnosis was associated with a lower occurrence of poor disease control. However, when initial TSH levels were controlled for in the analysis, this result became inconclusive although still favoring protection. The retrospective nature of the study did not allow us to periodically assess control of CH at fixed time intervals. The biochemical control in the study was limited to a one time evaluation which varies among the study participants: the earliest assessment was done at 4 months while the latest was when the child was 8.5 years old.

Stunting was observed in 24% of study participants. While many factors can affect growth in general, including genetics, nutrition and socioeconomic factors, early treatment, appropriate L-thyroxine dose and good compliance are factors associated with good final adult height in patients with CH.[7,15] Our results showed similar prevalence of stunting 14/55 (25%) in the early and late treatment groups 7/31(22%). Possible reasons include variations in initial dosages of L-thyroxine (4-15 mcg/kg/day) and compliance with treatment. Poor compliance with treatment can be deduced from the lack of information recorded on physician data sheets during regular clinic visits. Low parent's education was found to be a risk factor for stunting independent of the effects of early treatment, initial or continuing specialist co-management, control of disease. Low socioeconomic status of the child's family has also been reported as a possible risk factor for poor control of CH. Poor understanding of the condition and financial difficulties of the child's family contribute to poor compliance with treatment regimens, clinic visits and biochemical monitoring.[7,9]

The 16.5% prevalence of low overall IQ or DQ in this study is lower than the 25.8% reported by Kreisner, et al[14] in a study of Brazilian children. In other studies, however, 80-90% of CH patients treated with high dose L-thyroxine before 2 weeks of age have been reported to have IQs greater than 85,[1,5] although some may still have had learning and language difficulties or behavior problems.[3,5,8,9,16] The effect of poor biochemical control on the cognitive performance of the patients at the time of assessment has been reported to affect processing speed and cognition.[13] In our study, the association of poor control of disease with overall delay in neuro-development was inconclusive. Similar inconclusive results were obtained for early diagnosis (and treatment) and specialist care.

While the prevalence of overall cognitive delay was low, 54.4% of the participants had deficiency in at least one component of the FSIQ or DQ, particularly expressive language deficits or processing delays. While the results for overall cognitive delay were inconclusive, early diagnosis and treatment were found to be protective (ORa = 0.19) of delay in at least one component. In our study, children with cognitive delays in at least one aspect (i.e. verbal IQ, performance IQ, processing speed quotient or perceptual reasoning, working memory index) were older at the time of assessment than the children without delay by 14 months on the average. Older children are expected to achieve higher development, hence those evaluated at an older age may manifest more delays as a result of more "skills" being assessed. This is why in the logistic regression analysis, age at assessment was included to statistically adjust for the fact that the participants were assessed at different ages. Further, study participants with cognitive delays had higher initial TSH levels. Thus, TSH levels were also included in the analysis. Bargagna, et al[21] showed similar single aspect cognition delays (expressive language or phonological impairment) in 50% of their 3-year-old CH patients, and these delays persisted until the age of 5 years. Upon retesting the same patients at age 7 years, only 29% had the phonological impairment. In a cohort of 31 patients with CH, 25.8% had intellectual deficits at the age of 4 years. Low pretreatment T4, fewer clinic visits during the first year of life and low maternal schooling were cited as factors correlating with poor full scale intelligence quotient scores.[14]

Our study is an assessment of the prevalence of biochemical control, stunting and cognitive delay among CH patients identified through newborn screening. There was an attempt to identify protective and risk factors for these outcomes. However, during the conduct of the study, we encountered barriers (wrong patient contact information, no forwarding addresses, bogus addresses and phone numbers, incomplete patient data) in recalling patients for follow-up assessment, especially those older than the first 3 months of life. The standard of care and compliance with prescribed medications, clinic visits and biochemical monitoring were varied making comparisons among patients difficult. In 17% (15/86) of patients, information on timing of diagnosis and specialist care were missing. In these cases, we made an assumption that absence of information meant late diagnosis and absence of specialist care.

Our study has a number of limitations. The low percentage of participation resulted in a small sample that is not representative of the newborn population that was screened for CH. The retrospective nature of the study brought in recall bias, non-uniformity of recorded data, different lab results from various diagnostic labs utilizing different techniques, and incomplete retrieval of information on etiology, biochemical parameters (initial and monitoring thyroid hormone profiles). It also meant that the subjects

would be assessed at various times hence as mentioned earlier, cognitive delays would more likely be detected in the older children compared to the younger patients. On the issue of stunting as an outcome of CH, there are factors that we did not include in the analysis such as genetics, nutrition, or bone age at birth which affect final adult height.

However, inspite of these limitations, our study stressed the need for long-term newborn screening follow-up guidelines aimed at ensuring consistent monitoring and compliance of confirmed CH patients. Confirmed CH patients must be periodically contacted and assessed to confirm their compliance with treatment regimens. Without such tracking and monitoring, the likelihood of poor disease outcomes is high. Better mechanism for collecting and managing data on etiology of the CH detected, initial dosages of L-thyroxine, compliance with intake of medication, results of clinic visits, nutritional and socio-economic status, and physical and cognitive parameters must be developed if we are to meaningfully determine factors affecting outcome in CH children. If newborn screening is to be productive, disease outcomes must show significant improvements in the indicators that describe successful outcome. It will be important for specialists treating these children to agree on these indicators and how they should be monitored, including a recommended clinic visitation schedule for diagnosed newborns. Newborn screening program administrators consulting with specialists should determine strategies for improving treatment compliance, including compliance with the prescribed schedule of clinic visits necessary to ensure optimal growth and development.

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