Intellectual outcome in children with early treated congenital hypothyroidism

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Abstract

Background: Congenital hypothyroidism (CH) is one of the preventable causes of intellectual disability. L-thyroxine is a drug of choice for CH treatment to preserve normal brain development and function.

Objective: is to evaluate intellectual outcomes at preschool age in early treated CH.

Materials and methods: This retrospective chart review was conducted on 27 treated children with CH identified by neonatal screening program in Thailand from 1998 to 2017. The IQ test was performed at aged 6-8 years. Clinical data including sex, birth weight, age at the initiation of L-thyroxine, level of Free T4 and TSH before treatment, initial dose of L-thyroxine, type of CH, aged at IQ test, full scale IQ, verbal IQ and performance IQ were reviewed.

Results: Of 27 CH children, 7 patients were initially early treated with L-thyroxine before aged 14 days and 20 patients were treated after aged 14 days. Initial free T4, TSH, weight at treatment and initial dose of L-thyroxine were not different between early and late treatment group. Mean full scale IQ difference between 2 groups was statistic significantly (p=0.01). However, there was no statistically significant difference in the mean of verbal IQ and performance IQ. Thyroid scan results show dyshormonogenesis (n=12), thyroid agenesis/hypoplasia (n=5), and ectopic (n=10) Mean full scale IQ in dyshormonogenesis group was more than thyroid agenesis/hypoplasia and ectopic thyroid group. We found that timing at treatment and type of CH were independent factors significantly influencing the intellectual outcome (full IQ score≥90). (p=0.01)

Conclusion: Children with CH treated early after newborn screening within 14 days have better IQ score compare to CH treated after 14 days. Timing of treatment and type of CH have a role in neurodevelopment and intellectual outcome in CH children.

Introduction

Congenital hypothyroidism (CH) is one of the most treatable endocrine diseases of childhood. The incidence of CH worldwide is approximately 1:2,000 to 1:7,000 live births.[1-10] Failure to detect CH before the age of 3 months results in a high incidence of mental retardation. Thailand has introduced neonatal thyroid screening program since 1990. Early on, thyroid screening was conducted only in the University hospital. Furthermore, the ministry of public health has had a pilot study in neonatal thyroid and phenylketonuria screening program in the Northern, North-eastern and Southern parts of Thailand. Hat Yai Hospital, that is a 640-bed hospital under the control of the Ministry of Public Health in the Southern part of Thailand, has been established neonatal screening for congenital hypothyroidism and phenylketonuria program since 1998.

Treatment with thyroid hormone (L-thyroxine) in CH has been established worldwide to prevent mental retardation. Not

only early CH detection but also appropriate thyroid hormone dosage is very important to preserve normal brain development and function. Several studies shows some factors affect the intellectual outcome in CH such as high dose of L-thyroxine treatment, duration of TSH level normalization and initial time of L-thyroxine starting.[11-12] Although, high dose of L-thyroxine may increase the risk of craniosynostosis and neurological symptoms, there was no effect on cognitive outcome at 11 years of age.[13-14]

In this retrospective chart review study, we have evaluated intellectual outcomes at preschool age in CH after treating with L-thyroxine and several factors affecting IQ score.

Materials and methods

From 1998 to 2017, 77,243 neonates born at Hat Yai hospital were screened for CH. Infants with elevated TSH level of greater than 25 mIU/mL were recalled for evaluated serum free T4 and TSH level. If free T4<1.96 (ng/dL) and TSH>25 mIU/mL, it was newly diagnose of CH by pediatric endocrinologist. All children diagnosis as having CH immediately have started oral L-thyroxine and follow up free T4 and TSH including clinical evaluation with examination every 2-3 months. Thyroid scan and uptake were performed in affected infant after treatment at aged 3 years. The results are classified to normal/ dyshormonogenesis, thyroid agenesis/ hypoplasia or ectopic thyroid. Thai Wechsler Intelligence Scale for children (T-WISC) was done at aged 6-8 years in CH children. Full scale intelligence quotient (FIQ), verbal IQ (VIQ) and performance IQ (PIQ) were described. Full scale IQ was classified as follows: ≤69 is extremely low, 70-79 is borderline, 80-89 is low average, 90-109 is average, 110-119 is high average, 120-129 is superior and ≥130 is very superior[15].

Clinical data collections are sex, birth weight, aged at received L-thyroxine, initial Free T4 and TSH before treatment, initial dose of L-thyroxine (mg/kg/d), type of CH, age at IQ test, full scale IQ, verbal IQ and performance IQ. We follow up at least 6-8 years each child.

Children at increased risk of developmental problems for example preterm infant, birth asphyxia, congenital malformation and chromosome abnormalities, central hypothyroidism were excluded from this study. The ethical approval of this research was given by the research ethics committee of Hatyai hospital. Statistical analysis: Descriptive data summarized as means±standard deviation (SD). Unpaired Student's t-test was performed for 2 groups with normal distribution including weight at treatment, initial dose of L-thyroxine, age at IQ test (yr), full scale IQ, verbal IQ and performance IQ. Factors influence intellectual outcome (full IQ score≥90) by logistic regression analysis using STATA 13.0.

Results

Of 34 children with CH diagnose by neonatal screening, 27 who underwent IQ testing were included in this study, 17 (62.96%) were female and 10 (37.04%) were male. Mean weight at treatment was 3.75±0.35 kg. (3.20-4.33). Treatment with L-thyroxine was started after a mean of 28.9+37.3 days (7-180) at a mean initial dose of 9.2±1.8 mg/kg/d. Thyroid scan results showed 12 were dyshormonogenesis, 5 were thyroid agenesis/hypoplasia and 10 were ectopic thyroid gland. T-WISC for intellectual outcome was performed in 27 children at a mean age of 6.3±0.6 years (6-8). The mean IQ score was 85.7±14.2(58-112); the mean VIQ score was 81.7±14.3(54-108) and the mean PIQ score was 92.9±13.9(65-120). (Table 1)

Table 1 demographic and clinical data in patients with congenital hypothyroidism

Variable	Total (n= 27)	Female (n=17)	Male (n=10)
Birth weight (g)	3.06±0.19	3.09±0.20	3.04±0.19
Age at treatment (day)	28.9±37.3	25.5±25.1	35.4±54.8
Pretreatment Free T4 (ng/dL)	0.49±0.36	0.56±0.43	0.37±0.17
Pretreatment TSH (μIU/mL)	89.02±40.26	89.9±44.8	87.5±33.3
Weight at treatment (kg)	3.75±0.35	3.82±0.31	3.65±0.44
Initial dose of L-thyroxine (μg/kg/d)	9.2±1.8	9.29±2.06	9.12±1.75
Type of congenital hypothyroidism			
1. dyshormonogenesis	12	6	6
2. thyroid agenesis/ hypoplasia	5	3	2
3. ectopic	10	8	2
Aged at IQ test (yr)	6.3±0.6	6.2±0.3	6.4±0.7
Full scale IQ	85.7±14.2	83.4±11.6	89.6±17.7
Verbal IQ	81.7±14.3	80.0±12.3	84.7±17.5
Performance IQ	92.9±13.9	89.6±11.2	98.6±16.8

An IQ score above average was measured in 11 patients (90-112); 15 patients had an IQ score below 90 (70-86). (Table 2) Three had intellectual disability (defined as IQ<70) because of delayed CH detection. They has diagnosed as having CH at 1, 3, 6 month of age. Two moved on to other provinces, one had false negative neonatal screening. Type of CH was one agenesis and two ectopic thyroids.

Table 2 Full scale IQ in treated congenital hypothyroidism

Full Scale IQ	Number (%)
<69 (extremely low)	3 (11.1)
70-79 (borderline)	5 (18.5)
80-89 (low average)	8 (29.6)
90-109 (average)	10 (37.1)
110-119 (high average)	1(3.7)

Of 27 children, 7 patients were initial early treated before aged 14 days and 20 patients were treated after aged 14 days. Initial free T4, TSH, weight at treatment and initial dose of L-thyroxine were not difference between early and late treatment group. Mean full scale IQ was statistic significantly different between 2 groups (p=0.01). However, there was no statistically significant difference in the mean of verbal IQ and performance IQ. (Table 3)

Table 3 Comparison of intellectual outcomes in congenital hypothyroidism in early and late treatment group

Variable	Early treatment (start L-thyroxine before aged 14 day) (n=7)	Late treatment (start L-thyroxine after aged 14 day) (n=20)	p-value
Pretreatment Free T4 (ng/dL)	0.56±0.62	0.46±0.24	0.58
Pretreatment TSH (μIU/mL)	104.29±44.32	143.68±209.65	0.68
Weight at treatment (kg)	3.70±0.47	3.90±0.28	0.33
Initial dose of L-thyroxine (μg/kg/d)	10	9.22±1.84	0.40
Age at IQ test (yr)	6.41±0.77	6.30±0.56	0.68
Full scale IQ	99.82±10.81	80.75±11.83	0.01
Verbal IQ	90.66±8.08	84.66±4.61	0.32
Performance IQ	96.66±8.08	97.33±7.51	0.93

Further analysis of etiology was determined by thyroid scan: normal or dyshormonogenesis (n=12), thyroid agenesis/hypoplasia (n=5), and ectopic thyroid (n=10) Mean full scale IQ in dyshormonogenesis group was more than thyroid agenesis/hypoplasia and ectopic group. (Table 4)

Table 4 IQ test in congenital hypothyroidism by etiology (thyroid scan)

Type of congenital hypothyroidism	Dyshormonogenesis (n=12)	Thyroid agenesis/ hypoplasia (n=5)	Ectopic thyroid (n=10)
Full scale IQ (mean+SD, min-max)	96.9±9.4 (86-112)	76.0±12.5 (62-92)	77.1±10.2 (58-86)
Verbal IQ	92.3±9.3 (82-108)	74.0±16.9 (58-98)	72.9±10.2 (54-82)
Performance IQ	104.5±9.7 (92-120)	82.2±7.5 (75-93)	84.5±10.2 (65-93)

Age at treatment and type of CH were influence intellectual outcome (full IQ score≥90) by statistical significantly. (p=0.01, p=0.01) (Table 5)

Table 5 Factors influence intellectual outcome (full IQ score≥90)

Intellectual outcome	OR	95% CI	p-value
Sex	3.6	0.69 – 18.55	0.12
Age at treatment	17.9	1.7 – 118.1	0.01
Type of CH	70	5.5 – 88.2	0.01

Discussion

TSH screening for congenital hypothyroidism, using dried blood spot at the age of 2 days or older, is performed in accordance with the guideline for neonatal hypothyroid screening. The coverage rate of TSH screening is nearly 100% at Hat Yai hospital. The incidence of CH at Hat Yai hospital is 1:3,678 live-births. (data not publish) Problems that were found with the neonatal screening were loss to follow up, lack of knowledge, system error and funding. Our study suggested that whether the children with CH had normal or impaired neurodevelopment outcome depends on many factors. Of 27 patients, 11(40.8%) has normal full scale IQ (≥90) while 16(59.3%) has IQ score below average. Three had intellectual disability (defined as IQ<69) because of delayed CH detection at 1, 3 and 6 month of age. The cause of delayed in diagnosis were migration and false negative neonatal screening at a few days of life. Rahmani et al[16] found none of the treated CH children at first weeks after birth had IQ <70 at 6 years of age. Early detection and initial L-thyroxine started were very important. Children with CH have improvement in IQ after timely detection and treatment. They suggested start L-thyroxine within 7 days after birth to prevent intellectual deficit.

Our results showed that the timing of initial treatment significantly influenced full IQ score leading to intellectual outcome. Seven CH patients who had started with oral L-thyroxine before the age of 14 days have normal full scale IQ (≥90) at aged 6-8 years. Although, the results indicated lower mean IQ scores of CH in late treatment group (start L-thyroxine after aged 14 days), the success rate of CH detection and treatment at first to second weeks after birth is high because mean IQ scores of all cases at aged 6-8 years were within normal range. Verbal IQ and performance IQ scores between early and late treated groups were not significantly different similar to previous study[14-15]. Seo, et al[14] reported IQ scores of 5 to 7 year old children with early treated CH were also within normal range, regardless of etiology, thyroid function, initial dose of L-thyroxine and age at start of treatment.

Some studies indicate that several factors such as the severity of CH at diagnosis (defined by initial L-thyroxine at the moment of diagnosis and by skeletal maturation), poor compliance to replacement therapy during follow up might affect intellectual outcome[16]. In this study, we showed that the type of CH (dyshormonogenesis or thyroid agenesis/hypoplasia and ectopic thyroid) is a main risk factor in IQ deficit. These are consistent with many previous studies[13-17]. Regarding the factors influencing intellectual outcome (full IQ score≥90), univariate analyses showed a significant difference in age of treatment and type of CH and multivariate regression analysis can't be performed due to small number of data. Nevertheless, in this study we identify independent factors (age of treatment and type of CH) associated with full IQ score≥90. Rovet[17] showed that children with CH (dysgenetic gland) treated early in life may have reduced IQ compare to CH (dyshormonogenesis). However, some study showed none of the factors influencing neurodevelopment and intellectual outcome in preschool age CH children[15]. We suggested early diagnosis and treatment with appropriate dose of L-thyroxine in CH children to improve intellectual outcome. Although, type of CH may effects intellectual outcome at preschool aged.

Summary

Early treating with L-thyroxine within 14 days of age provides better IQ score compare to late treatment (after 14 days of age). Early diagnosis and treatment of CH with L-thyroxine as well as patients' compliance can prevent deficit in neurodevelopment and improve intellectual outcome in CH children.

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ผลลัพธ์ทางสติปัญญาในเด็กที่ได้รับการรักษาตั้งแต่แรกในผู้ป่วยภาวะพร่องไทรอยด์ฮอร์โมนแต่กำเนิด

ปฏิการ ดิสนีเวทย์

บทคัดย่อ

ความเป็นมา: ภาวะขาดไทรอยด์ฮอร์โมนแต่กำเนิดเป็นสาเหตุหนึ่งที่สามารถป้องกันความพิการทางสติปัญญา การรักษาด้วยยา L-thyroxine สามารถทำให้สมองมีพัฒนาการและการทำงานที่ปกติ

วัตถุประสงค์: เพื่อศึกษาผลของสติปัญญาในผู้ป่วยขาดไทรอยด์ฮอร์โมนแต่กำเนิดที่ได้รับการรักษาระยะแรกในช่วงก่อนวัยเรียน

วัสดุและวิธีการ: การศึกษาแบบย้อนหลังจากเวชระเบียนผู้ป่วยที่มีภาวะขาดไทรอยด์ฮอร์โมนแต่กำเนิดจำนวน 27 ราย วินิจฉัยจากโปรแกรมการตรวจคัดกรองในทารกแรกเกิดระหว่างปี พ.ศ.2541 - พ.ศ. 2560 ที่ได้รับการตรวจระดับทางสติปัญญา (IQ test) ที่อายุ 6-8 ปี ข้อมูลที่ศึกษาประกอบด้วย เพศ น้ำหนักแรกเกิด อายุที่เริ่มให้ยา L-thyroxine ระดับ Free T4 และ TSH ก่อนรักษา ขนาดยา L-thyroxine ที่เริ่มรักษา ชนิดของภาวะขาดไทรอยด์ฮอร์โมนแต่กำเนิด อายุขณะที่ตรวจ IQ test ผล IQ test ประกอบด้วย full scale IQ, verbal IQ และ performance IQ

ผลการศึกษา: ผู้ป่วยภาวะขาดไทรอยด์ฮอร์โมนแต่กำเนิด 27 ราย พบว่า 7 รายได้รับการรักษาด้วย L-thyroxine ก่อนอายุ 14 วัน 20 รายได้รับการรักษาด้วย L-thyroxine ที่อายุมากกว่า 14 วัน ระดับ free T4, TSH น้ำหนักขณะเริ่มรักษา ขนาดยา L-thyroxine ที่เริ่มรักษาไม่แตกต่างกันระหว่าง 2 กลุ่ม ค่าเฉลี่ยคะแนน full IQ มีค่าแตกต่างกันระหว่าง 2 กลุ่มอย่างมีนัยสำคัญทางสถิติ (p=0.01) แต่ไม่พบความแตกต่างของ verbal IQ และ performance IQ ของทั้ง 2 กลุ่ม ผล thyroid scan พบ dyshormonogenesis 12 ราย agenesis/hypoplasia 5 ราย ectopic 10 ราย ค่าเฉลี่ยคะแนน full IQ ในกลุ่ม dyshormonogenesis สูงกว่ากลุ่มที่เหลือ การศึกษานี้พบว่า อายุที่เริ่มให้การรักษาและชนิดของภาวะขาดไทรอยด์ฮอร์โมนมีผลต่อพัฒนาการทางสติปัญญาปกติ (full IQ score≥90) อย่างมีนัยสำคัญทางสถิติ (p=0.01)

สรุป: ผู้ป่วยเด็กที่มีภาวะขาดไทรอยด์ฮอร์โมนแต่กำเนิดได้รับการรักษาก่อนอายุ 14 วัน พบว่ามีค่าระดับสติปัญญาปกติเมื่อเปรียบเทียบกับกลุ่มที่ได้รับการรักษาหลังอายุ 14 วัน ระยะเวลาที่ให้การรักษาและชนิดของภาวะขาดไทรอยด์ฮอร์โมนแต่กำเนิดมีบทบาทสำคัญต่อพัฒนาการทางสติปัญญาของผู้ป่วย

กลุ่มงานกุมารเวชกรรม โรงพยาบาลหาดใหญ่ สงขลา 90110