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Thyroid Function of Asphyxiated Newborns who Received Hypothermia Therapy

Short running title: Thyroid Function of Asphyxiated Newborns

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Abstract

Background: Thyroid function of asphyxiated newborns who received hypothermia therapy and its relation to neurological outcome are not well described.

Methods: This is a prospective study measuring thyroid function of 12 asphyxiated newborns who received hypothermia therapy. We measured serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels on admission, 24, 72, and 96 hours after birth, and at discharge (17-54 days). Twelve newborns were divided into two groups based on the presence of brain injury on head magnetic resonance imaging findings (six in the abnormal imaging group and six in the normal imaging group) and their thyroid functions were compared between the two groups.

Results: Serum TSH levels were within a normal range. Serum FT3 and FT4 levels remained low at 24, 72, and 96 hours after birth, and returned to a normal range at discharge. There was no significant difference in serum TSH levels between the two groups. However, serum FT4 levels at 72 hours after birth, and serum FT3 and FT4

levels at 96 hours after birth were significantly lower in the abnormal imaging group than those in the normal imaging group ($p = 0.03$, $p = 0.02$, and $p = 0.01$, respectively). Conclusion: These results suggest that asphyxiated newborns have transient low thyroid hormone levels at 24-96 hours after birth. Serum FT3 and FT4 levels between 72 and 96 hours after birth may predict brain injury of asphyxiated newborns.

Background

Severe neonatal asphyxia can cause hypoxic-ischemic encephalopathy (HIE). Asphyxiated newborns with moderate or severe HIE can cause severe neurological disability, or die.[1-3] Severe hypoxemia affects brain as well as important organs, such as heart, lung, liver, and intestine, etc. A previous study reported that thyroid function was lower in asphyxiated newborns, especially those with moderate or severe HIE, than in non-asphyxiated newborns between 18 and 24 hours after birth.[4] However, there have been limited reports on the temporal transition of thyroid function after 24 hours of age in asphyxiated newborns. Additionally, the relationship between thyroid function of asphyxiated newborns and long-term neurological outcome is unknown.

Therefore, this study aimed to investigate the temporal transition of thyroid function, and the relationship between thyroid function and neurological outcome in asphyxiated newborns with moderate or severe HIE who received hypothermia therapy.

Methods

Study subjects

We enrolled 12 asphyxiated newborns with moderate or severe HIE who received hypothermia therapy in the General Center for Perinatal, Maternal and Neonatal Medicine, Niigata University Medical and Dental Hospital between October 2010 and March 2013. We measured serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels to evaluate their thyroid function, which was measured on admission, at 24, 72, and 96 hours after birth, and at the time of discharge. Blood samples at 24 and 72 hours after birth were collected during the hypothermia therapy. Serum TSH, FT3, and FT4 levels were measured by an electrochemical luminescence immunoassay.

Because we were not able to have normal newborns as a control group in this study, we used serum thyroid hormone levels of healthy Japanese newborns during the first week of life as controls.[5] Because the timing of blood sampling at discharge were different (17-54 days), serum TSH, FT3, and FT4 levels at the time of discharge were compared with thyroid hormone levels of healthy Japanese newborns at 168 hours after birth.

Brain imaging

We divided the 12 newborns into two groups based on the presence of signs of brain injury on head magnetic resonance imaging (MRI) at discharge (e.g., multicystic encephalomalacia and/or lesions of the thalamus and basal ganglia). Six (50%) patients were classified as the abnormal imaging group and the rest of six (50%) patients were classified as the normal imaging group, which showed normal findings on MRI. The MRI findings were evaluated by radiologists. We compared perinatal factors and thyroid function between the two groups.

This study was approved by the ethics committee of Niigata University School of Medicine and informed consent was obtained from the patients' family when the patients were enrolled in the study.

Hypothermia therapy

Hypothermia therapy was performed when the patients were admitted to our neonatal intensive care unit (NICU). They satisfied all of the following five criteria: (1) born at 36 weeks or longer gestation with a birth weight of 2000g or above; (2) Apgar score of

5 or less at 10 minutes after birth and patients required assisted ventilation at birth; (3) moderate or severe HIE; (4) cord blood pH less than 7.0 or serum lactate levels of the newborn more than 70 mg/dl; (5) admitted to the NICU within 6 hours. We performed selective head cooling using the Medicool MC-2100 (Mac8, Yokohama, Japan). The rectal temperature was lowered to 34.0 degrees and maintained for 72 hours. Mechanical ventilation, administration of dopamine and dobutamine, and midazolam treatment were performed during the cooling period, but enteral feeding was not performed. After 72 hours of hypothermia, we rewarmed newborns to 36.5 degrees with the speed of 0.4 degrees per hour. Importantly, dopamine could suppress thyroid function,[6] so that we compared the average daily dosage of dopamine from birth to 4 days after birth between the two groups. New indication criteria of hypothermia therapy based on CoSTR 2010 is currently recommended in Japan.[7] All of the patients in this study also met the new indication criteria.

Statistical analysis

The data were analyzed with the Fisher's exact test for categorical variables and with

the Wilcoxon rank sum test for continuous variables. P values <0.05 were considered significant. Analysis was performed using the JMP Pro version 10 for Windows (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics

The background characteristics of the patients is shown in Table 1. The number of the patients with severe HIE was significantly higher in the abnormal imaging group than in the normal imaging group (p = 0.014). There were no significant differences in the other characteristics between the two groups. Of note, none of the patients' mothers had thyroid diseases.

Thyroid function of asphyxiated newborns

Serum TSH levels in all asphyxiated patients were high on admission, however, it went down to the lower limit of normal range at 24 hours (**Figure 1**). Serum TSH levels remained close to the normal range at 72 and 96 hours after birth, and at the time of discharge (**Figure 1**). Only one newborn had a delayed increase in TSH levels at the

time of discharge (51.17 μIU/ml) and was treated with levothyroxine sodium. Serum FT3 and FT4 levels were normal or high on admission, but these levels remained low at 24, 72, and 96 hours after birth. Serum FT3 and FT4 levels returned to a normal range at the time of discharge **(Figures 2 and 3)**.

Thyroid function and neurological outcome

We compared thyroid function between the two groups. There was no significant difference in serum TSH levels between the two groups (**Figure 4**). However, serum FT4 levels at 72 hours after birth, and serum FT3 and FT4 levels at 96 hours after birth were significantly lower in the abnormal imaging group than those of the normal imaging group ($p = 0.026$, $p = 0.023$, and $p = 0.010$, respectively) (**Figures 5 and 6**).

Next, we compared the average daily dosage of dopamine between the two groups. The average dosage of dopamine on day 1 was significantly higher in the abnormal imaging group than that of the normal imaging group ($p = 0.031$) (**Table 2**). There were no significant differences in the average dosage of dopamine on days 0, 2, 3, and 4 between the two groups.

Discussion

Neonatal asphyxia can cause hypothyroidism in the early period after birth.[8-10] However, there have been few reports on the temporal transition of thyroid function after 24 hours of age in asphyxiated newborns. With regard to the reports of thyroid function in asphyxiated newborns, only one report described whether asphyxiated newborns have HIE.[4] Consequently, the relationship between thyroid function of asphyxiated newborns and neurological outcome is unknown. Thus, we evaluated the temporal transition of thyroid function, and the relationship between thyroid function and neurological outcome in asphyxiated newborns with moderate or severe HIE who received hypothermia therapy. In this study, we found that asphyxiated newborns who received hypothermia therapy had transient hypothyroidism between 24 and 96 hours after birth. Serum TSH levels were low at 24 hours after birth, and serum FT3 and FT4 levels were low at 24, 72, and 96 hours after birth. One study reported that asphyxiated newborns had transient hypothyroidism after birth, and their thyroid function recovered by 15 days after birth.[11] Our findings was similar to their report, but one newborn in our

study had a delayed increase in TSH levels at the time of discharge. This patient was born at 36 weeks of gestational age and was classified into the normal imaging group. We speculated that premature birth might be one of the reason for a delayed increase in TSH levels; however, the detailed mechanisms are unknown. Therefore, thyroid function evaluation may be needed at least once before discharge in asphyxiated newborns who received hypothermia therapy.

We compared thyroid function between the two groups. We found that serum FT3 levels at 96 hours after birth, and serum FT4 levels at 72 and 96 hours after birth were significantly lower in the abnormal imaging group than those of the normal imaging group. Serum FT4 levels at 96 hours after birth were strongly associated with abnormal imaging. To the best of our knowledge, there is no report describing this finding, which suggests that evaluating thyroid function between 72 and 96 hours after birth may be able to predict the presence of abnormal imaging, which may reflect brain injury in asphyxiated newborns who received hypothermia therapy. Further investigation is necessary given the numbers of cases are limited in the current study.

The cause of transient hypothyroidism in asphyxiated newborns is called non-thyroidal illness syndrome (NTIS), which is a clinical condition in which serum thyroid hormone levels are abnormal, although thyroid disease is unapparent. Starvation, systemic illness, and medications are known to the causes of NTIS.[12] Initially, only serum T3 and FT3 levels decrease in patients with NTIS. As the severity of the illness increases, serum T4 and FT4 levels decrease. Of note, serum TSH levels are low or normal in patients with NTIS. If this illness improves, these serum thyroid hormone levels also improve. In the present study, these serum thyroid hormone levels changed in a similar manner to NTIS. Therefore, we speculated that severe systemic illness due to neonatal asphyxia caused NTIS, and subsequently transient hypothyroidism occurred.

The medications, such as dopamine or corticosteroids cause NTIS.[13] We administered dopamine to all patients in the current study. We showed the average dosage of dopamine on day 1 was significantly higher in the abnormal imaging group than that of the normal imaging group. However, there was no significant difference in thyroid function on day 1 between the two groups. Therefore, we speculated that dopamine did

not affect their thyroid function.

Hypothermia can influence thyroid function. When the body temperature was low for a long time in adults, serum T4 and FT4 levels did not change; however, serum T3 and FT3 levels dropped.[14] However, in the current study, serum FT4 levels were low, as well as serum FT3 levels. Additionally, serum FT3 and FT4 levels at 96 hours after birth after rewarming remained low. Therefore, we speculated that NTIS caused transient hypothyroidism in our asphyxiated newborns.

The degree of decrease in serum T3 and FT3 levels was correlated with the severity of the illness, and the degree of decrease in serum T4 and FT4 levels was correlated with the probability of death.[12] In adults, when serum T4 levels drop below 2 μg/dl, the probability of death reaches 80%. No patients died in the current study, but serum FT4 levels at 72 and 96 hours after birth were significantly lower in the abnormal imaging group than in the normal imaging group. In particular, low serum FT4 levels at 96 hours after birth were strongly associated with abnormal imaging, which could lead to severe brain injury. This result suggests that serum FT4 levels at 96 hours after birth could be a

marker for predicting severe brain injury in asphyxiated newborns who received hypothermia therapy.

There are a few limitations to this study. First, the number of cases was small. Further studies including more cases are needed to confirm our novel findings. Second, the timing of blood sampling at discharge varied, ranging from 17 to 54 days after birth. Thus, the timing when thyroid function improved was unknown.

In conclusion, we found that asphyxiated newborns who received hypothermia therapy had transient hypothyroidism between 24 and 96 hours after birth. Serum FT3 and FT4 levels between 72 and 96 hours after birth can be a marker for predicting brain injury in asphyxiated newborns who received hypothermia therapy.

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Author contribution

AK, TU, and MW conceived and designed the study; AK, TU, TK, and KK collected the data; AK analyzed the data and wrote the manuscript; TU, MW, and AS critically reviewed the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Serum thyroid stimulating hormone (TSH) levels in patients who received hypothermia therapy. The bars indicate the mean ± SD levels of TSH. The grey bars indicate the reference levels of TSH in healthy Japanese newborns.

Figure 2. Serum free T3 (FT3) levels in patients who received hypothermia therapy. The bars indicate the mean ± SD levels of FT3. The grey bars indicate the reference levels of FT3 in healthy Japanese newborns.

Figure 3. Serum free T4 (FT4) levels in patients who received hypothermia therapy. The bars indicate the mean ± SD levels of FT4. The grey bars indicate the reference levels of FT4 in healthy Japanese newborns.

Figure 4. Comparison of serum thyroid stimulating hormone (TSH) levels between the abnormal imaging group and normal imaging group based on magnetic resonance imaging. The bars indicate the mean ± SD levels of TSH.

Figure 5. Comparison of serum free T3 (FT3) levels between the abnormal imaging group and normal imaging group based on magnetic resonance imaging. The bars indicate the mean ± SD levels of FT3.

Figure 6. Comparison of serum free T4 (FT4) levels between the abnormal imaging group and normal imaging group based on magnetic resonance imaging. The bars indicate the mean ± SD levels of FT4.

Table 1 Clinical characteristics of the study subjects

	Abnormal imaging group n = 6 Median (IQR) or n	Normal imaging group n = 6 Median (IQR) or n	P-value
Female	5	4	0.505
Gestational age (weeks)	39.4 (37.2 - 41.2)	38.3 (36.3 - 40.2)	0.448
Birth weight (g)	2644 (2407 - 3020)	2582 (2045 - 3171)	0.806
Apgar score 1min	1.0 (0.8 - 2.0)	1.0 (1.0 - 2.0)	0.664
Apgar score 5min	2.5 (1.5 - 4.3)	3.5 (2.8 - 4.0)	0.418
Small for gestational age	0	0	-
Cesarean section	5	4	0.505
Cord blood pH	6.67 (6.56 - 6.86)	6.98 (6.64 - 7.05)	0.221
Serum lactate on admission (mg/dl)	134.5 (95.8 - 165.3)	98.5 (78.0 - 124.8)	0.348
Sarnat classification	Moderate 2, Severe 4	Moderate 6, Severe 0	0.014
Head MRI abnormal findings			
multicystic encephalomalacia + lesions of thalamus and basal ganglia	2		
lesions of thalamus and basal ganglia	3		
focal brain necrosis	1		

IQR, interquartile range

Table 2 Average dosages of dopamine between the two groups

	Abnormal imaging group n = 6 Median (IQR)	Normal imaging group n = 6 Median (IQR)	P-value
Day 0	3.4 (2.7 - 5.0)	3.6 (2.7 - 4.9)	1.000
Day 1	5.1 (4.8 - 7.2)	4.0 (3.1 - 4.9)	0.031
Day 2	5.1 (4.1 - 8.4)	4.3 (3.7 - 5.1)	0.203
Day 3	3.3 (2.9 - 6.0)	4.6 (2.9 - 5.3)	0.972
Day 4	2.2 (1.0 - 3.7)	2.3 (0.9 - 3.0)	0.812

unit, μg/kg/min; IQR, interquartile range

Figure 1.

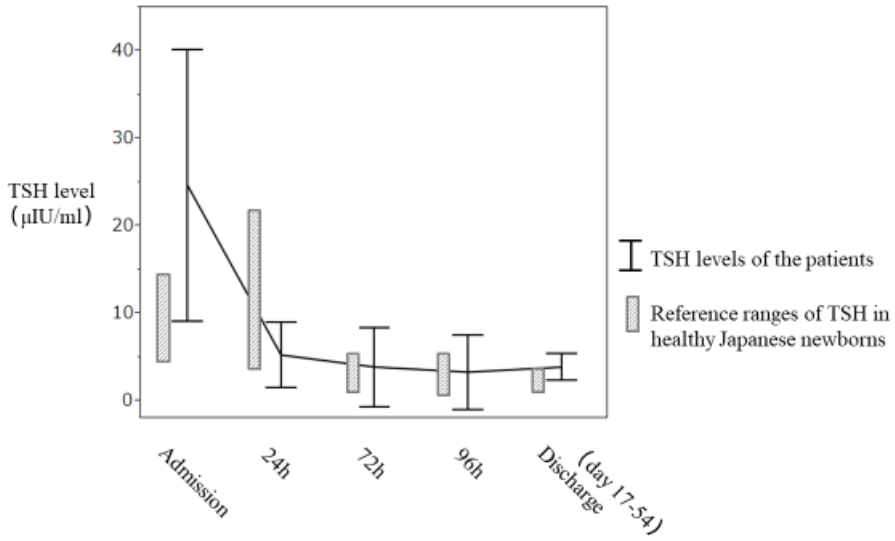

TSH level
(μIU/ml)
40
30
20
10
0
Admission
24h
72h
96h
Discharge
(day 17-54)
TSH levels of the patients
Reference ranges of TSH in healthy Japanese newborns

Figure 2.

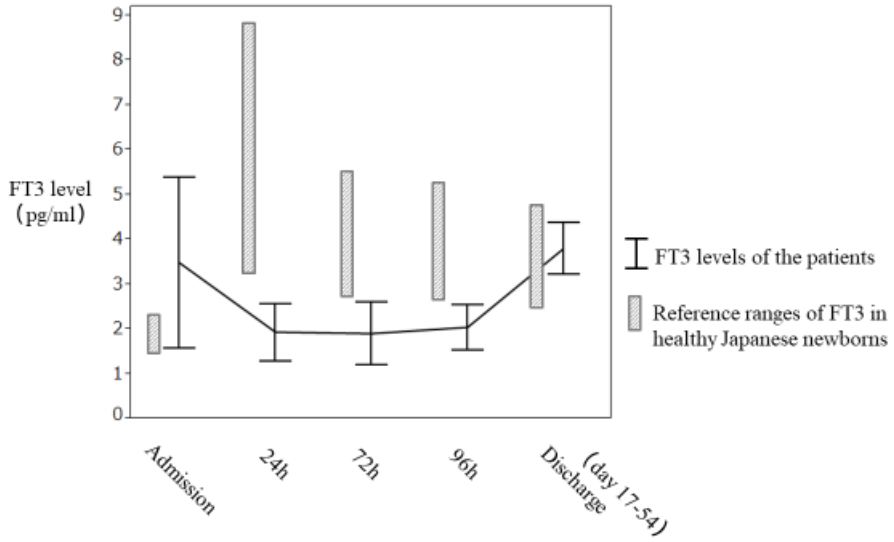

FT3 level
(pg/ml)
0
1
2
3
4
5
6
7
8
9
Admission
24h
72h
96h
Discharge
(day 17-54)
FT3 levels of the patients
Reference ranges of FT3 in healthy Japanese newborns

Figure 3.

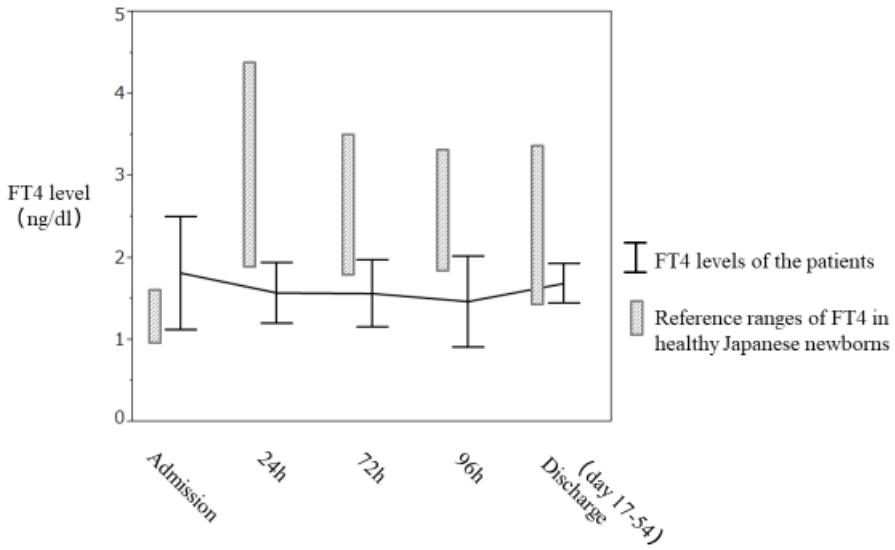

FT4 level
(ng/dl)
5
4
3
2
1
0
Admission
24h
72h
96h
Discharge
(day 17-54)
FT4 levels of the patients
Reference ranges of FT4 in
healthy Japanese newborns

Figure 4.

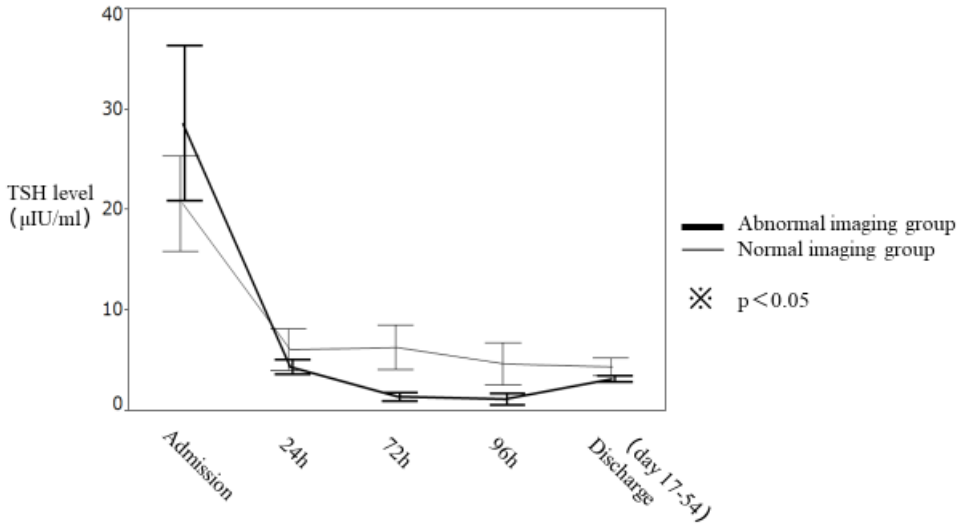

40
30
20
10
0
TSH level
(μIU/ml)
Admission
24h
72h
96h
Discharge
(day 17-54)
Abnormal imaging group
Normal imaging group
※ p＜0.05

Figure 5.

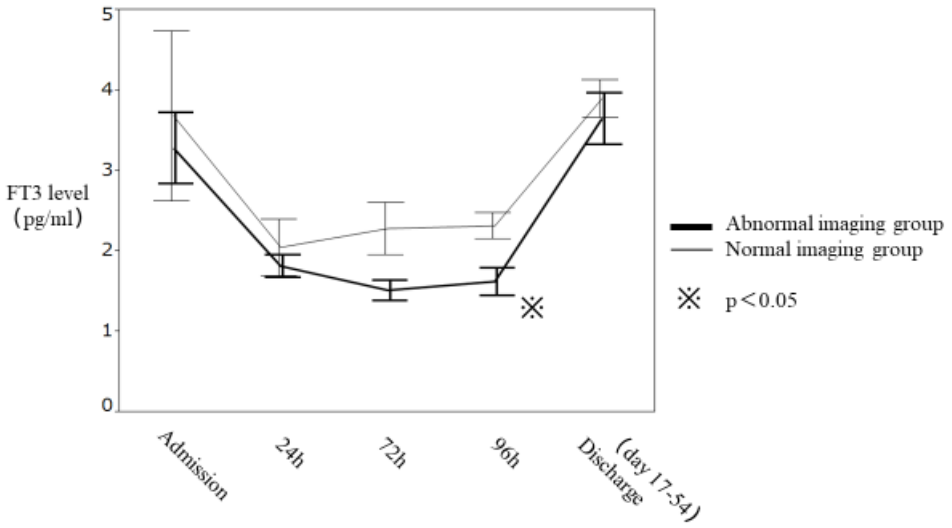
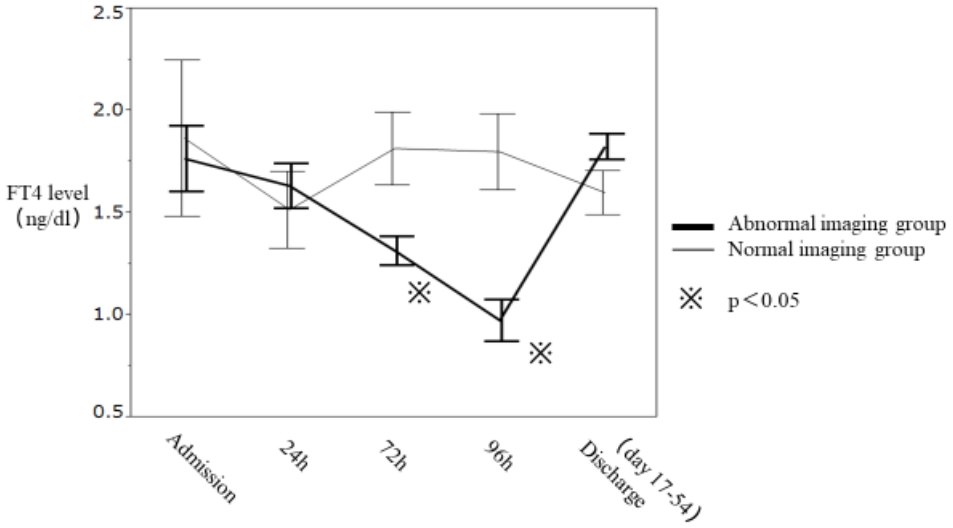

FT3 level
(pg/ml)
5
4
3
2
1
0
※
Admission
24h
72h
96h
Discharge
(day 17-54)
Abnormal imaging group
Normal imaging group
※ p＜0.05

Figure 6.


2.5
2.0
1.5
1.0
0.5
FT4 level
(ng/dl)
※
※
Admission
24h
72h
96h
Discharge
(day 17-54)
Abnormal imaging group
Normal imaging group
※ p＜0.05