Low T3 syndrome (LT), also called euthyroid sick syndrome or non-thyroidal illness syndrome, is a well-established condition. Low thyroid hormone levels, in particular low T3 levels, appear concomitantly with severe illness or starvation in this condition. Patients generally do not require thyroid hormone replacement therapy [1-5].

On the other hand, central hypothyroidism refers to a thyroid hormone deficiency due to a disorder of the pituitary, hypothalamus or hypothalamic-pituitary portal circulation, and is mostly caused by a coexisting/previous hypothalamic or pituitary disease/condition such as a brain tumor, cranial irradiation, or trauma [6, 7]. Patients with central hypothyroidism require thyroid replacement therapy. In addition, they usually have deficiencies of other pituitary hormones, such as ACTH and GH.

There exists no serological cut-off value at present to separate low T3 syndrome from central hypothyroidism, rendering a differential diagnosis between the two conditions sometimes difficult. This is especially the case when the patient is in a starved state or in a poor nutritional condition.

The fT3/fT4 is theoretically higher in central hypothyroidism than in low T3 syndrome. In central hypothyroidism, serum fT4 values are low but fT3 values typically within normal limits [5] whereas in low T3 syndrome fT3 values is low by definition and fT4 values may remain within the normal range, except in cases of a severe type of low T3 syndrome, in which the fT4 values also show a marked decrease [1, 4]. There have been no reports of the fT3/fT4 in these two conditions.

The purpose of this study was to analyze whether fT3/fT4 is useful in differentiating central hypothyroidism from low T3 syndrome.
Participants and Methods

We conducted a retrospective study from March, 1994 to May, 2014 at three tertiary hospitals. The participants were mostly from TMCMC with an exception of 10 children as you see below.

Participants (Fig. 1)

The first set of participants used to define arbitrarily the cut-off value of fT3/fT4 consisted of two patient groups comprising subjects from the age of 6 to 20 years at one institution (TMCMC), the ‘group CH (central hypothyroidism)’ and the ‘group A (anorexia nervosa)’, both of which were defined clinically in the charts of 1994-2014. The group A comprised 36 patients (2 boys and 34 girls) in whom anorexia nervosa was diagnosed. Brain tumor was refuted in all the patients in this group. The other inclusion criteria of this group was the obesity index (as defined below) under -20% and serum fT3 < lower limit for adults, or 2.3 pg/mL, indicating the patients of this group A were associated with low T3 syndrome. The group CH comprised 16 patients (8 boys and 8 girls) in whom central hypothyroidism was diagnosed on the basis of hormonal data, brain MRI, or genetic analysis.

The second set of participants, also from the age of 6 to 20 years, was recruited at TMCMC in order to validate the previously described cut-off value in the first set of participants (Fig. 2) in 2010-2014. The patients admitted the neonatal intensive care unit were excluded. The serum fT3, fT4, and TSH levels measured more than twice in the study (n = 2,348). The next selection criterion for this second set of the participants was an fT3 < 2.3 pg/mL or fT4 < 0.9 ng/dL in the results of their first blood test. As is shown in Fig. 2, the following patients were further excluded: 1) those with fT3 and fT4 values under the sensitivity of the measurements (n = 21); 2) those presenting complications or receiving drugs which may have influenced thyroid function (n = 157) [8-10] such as artificial dialysis, high dose corticosteroids (above 20 mg of prednisolone), amiodarone, antiepileptic agents such as carbamazepine, levothyroxine; and 3) those presenting a complication of a primary thyroid disease.

Among the final 229 patients of this second set of participants, group L (Fig. 1) consisted of patients (n = 58; 9 boys and 49 girls) in poor nutritional or physical status at the initial fT3, fT4, and TSH measurements. These patients were mostly those admitted in the intensive care unit and those with anorexia nervosa. fT3 and fT4 in this group normalized with improvement of their status, suggesting that this group represents patients with low T3 syndrome. Group C (Fig. 1) comprised 4 subjects in whom central hypothyroidism was diagnosed on the TRH stimulation test, brain MRI, or genetic analysis.

Fig. 1  The illustrations of the first and second sets of the participants
The age in these population was all from 6 to 20 years.
The third group of participants comprised group “L + A” (n = 125) and group “C + CH” (n = 27) at the same hospital. The definition of these groups of “L + A” and “C + CH” was done similarly to the groups of L, A, C and CH, respectively. The range of the age in these groups was at all ages less than 18 years. We added the double quotation marks before and after the names of the groups (like group “L + A” and group “C + CH”) in order to emphasize the age ranges were all ages less than 18 years. Similarly to the second set of the groups, the patients admitted in our neonatal intensive care unit were excluded. In the analysis, the overlapped participants of either group “L + A”, or group “C + CH” were counted only once.

The last, fourth set of the participants comprised a group of 10 central hypothyroidism patients seen at the other two hospitals.

**Methods**

1) On the basis of an analysis of the first set of participants, a cut-off value of fT3/fT4 was established to distinguish the group A from the group CH. The fT3/fT4 was calculated at the lowest point of the obesity index in the group A, and at the initiation of levothyroxine administration in the group CH.

2) An analysis of the second set of participants enabled us to validate the cut-off value determined by our analysis of the first set of participants. The sensitivity and specificity of group L and C for the cut-off value were determined.

3) In order to see the utility of the fT3/fT4 with age, the fT3/fT4 of group “L + A” (n = 125) and group “C + CH” (n = 27) was analyzed by our analysis of the third set of participants.

4) Finally, in order to evaluate the fT3/fT4 in central hypothyroidism cases in different cohorts (n = 10), fT3/fT4 was analyzed in the fourth set of participants who were above the age of 2 years at the samplings. They were finally treated with l-thyroxine.

**The obesity index**

The obesity index was calculated using height and standard body weight values (see Supplementary Tables 1 and 2) published in the List of School Health Statistical Survey Conducted by the Ministry of Education, Science and Culture in 2000 in Japan [9, 10]. With regard to BMI values, for a male or a female child above 6 years of age whose obesity index was -20%, the BMI was 14.9-20.8 and 14.9-20.36, respectively. The group A in our study was defined as having an obesity index under -20% because children under -20% are considered clinically pathological in Japan. There is no simple conversion formula for transforming the obesity index to the body mass index (BMI).
**Thyroid function**

The standard values of fT3, fT4, and TSH for adults at our treatment center are 2.3-4.3 pg/mL, 0.9-1.7 ng/dL, and 0.5-5.0 µIU/mL, respectively. Serum fT3, fT4, and TSH measurements in all participants, except for those ten as described below, were made with lumipulse fT3-III, fT4-N, TSH-III (Fujirebio, Tokyo Japan), all of which are commercially available kits. Intra-assay CVs of these three tests all fell under 10% in each physiological concentration.

fT3 and fT4, and TSH were assessed with another three sets of kits (Roche, Tokyo, Japan) in the fifth set of the ten participants. Conversion formulae, which had already been studied (Supplementary Table 3), were applied to transform fT3, fT4, and TSH Roche data of these ten children into the corresponding Fujirebio data so that all the data were considered to be unified in methodology in this study.

**Statistical data analysis**

The difference in the median value of fT3/fT4 between group A and CH was evaluated by two-sided Mann-Whitney’s U-test. The difference in the mean fT3/fT4 ratio between group “L + A” and group “C + CH” was examined by Student’s t test and Welch’s t test. Statistical analysis was performed using SSPA 22nd. A difference of \( p < 0.05 \) was considered significant.

**Ethics**

This study was approved by our ethical committee (H26-58).

**Results**

1) In the first set of participants with ages being 6 to 20 years, the fT3/fT4 of group A ranged from 0.88 to 3.4 with the median of 1.80. In group CH, the range was from 2.05 to 7.08 (median 3.48; see Table 1). The fT3/fT4 was statistically lower in group A than in group CH (\( p < 0.05 \)). The arbitrary cut-off value was set at 2.0 because there was no patient in the group CH whose fT3/fT4 was under 2.0 (Fig. 3).

2) In order to validate this cut off value, further analysis was done using the second set of participants, whose age range was also 6 to 20 years. In group L, the fT3/fT4 ranged from 0.8 to 4.0 and was less than 2.0 in 36 out of 58 patients, whereas in the non-L group it was less than 2.0 in 18 out of 171 patients (Table 2). The sensitivity of detection for group L was 62%, the specificity was 89%, the positive predictive value was 67%, and the negative predictive value was 87%. Seventeen out of 18 patients with a false positive were anorexia nervosa patients whose serum fT3 or fT4 had never been normal. Thus, these seventeen patients did not satisfy the criteria of group L (since they never recover from ‘low T3’ condition). The single remaining patient showed normal thyroid function with serum fT3 at 2.28 pg/mL. Taken together, the specificity of detection for group L was almost 100%.

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**Table 1** The fT3/fT4 of certain-L and -C groups

|         | n  | Minimum | Median | Maximum |
|---------|----|---------|--------|---------|
| Group A | 36 | 0.88    | 1.80   | 3.40    |
| Group CH| 16 | 2.05    | 3.48   | 7.08    |

*The unit of fT3 and fT4 are pg/mL and ng/dL, respectively.*

**Table 2** Numbers of the patients with fT3/fT4# being < or > 2 in group L and non-group L

|        | < 2 | > 2 | Total |
|--------|-----|-----|-------|
| Group L| 36  | 22  | 58    |
| Non-group L| 18  | 153 | 171   |
| Total  | 54  | 175 | 229   |

The sensitivity, specificity, positive predictive value and negative predictive value are 62%, 89%, 67% and 87%, respectively.  
# The unit of fT3 and fT4 are pg/mL and ng/dL, respectively.
The fT3/fT4 of the four patients in group C was over two, ranging from 3.5-5.2. Similarly, the sensitivity of detection for group C was 100%, the specificity was 24%, the positive predictive value was 2.3%, and the negative predictive value was 100% (Table 3).

3) In the next step, a possible age-dependency of the cut-off value was examined by analyzing the fT3/fT4 among group “L + A” at all ages (n = 125). The scatter graph shows the fT3/fT4 in group “L + A” according to age (Fig. 4). The mean values of those two groups under and over two years of age differed significantly at 3.40 and 1.89, respectively (p < 0.05). Therefore, the analysis of the fT3/fT4 of group “L + A” and group “C + CH” for patients younger than two years was treated separately from the analysis for those older than two years. At two years of age or younger, the fT3/fT4 was not significantly different (p = 0.324; mean = 3.40 and 3.69, respectively) between group “L + A” and the group “C + CH”. On the other hand, the fT3/fT4 between the two conditions significantly differed above two years (p < 0.05; mean = 1.89 and 4.01, respectively), indicating that the cut-off value of 2.0 could be used only with subjects older than two years. In other words, the cut-off value of fT3/fT4 < 2.0 is useful in ruling out central hypothyroidism above two years of age.

4) The fT3/fT4 in the fifth set of participants with central hypothyroidism ranged from 2.55 to 7.71 in total. When you excluded the two participants who had the risk factors for low T3 syndrome, the range was from 4.62 to 7.71 (Table 4).

**Discussion**

To the best of our knowledge, our study is the first to demonstrate the utility of fT3/fT4 in differentiating between central hypothyroidism and low T3 syndrome from the age of 2 to 18 years. When the value is under 2.0 at these ages, the possibility of central hypothyroidism is low. The role of the patient’s age in the differential diagnosis remains unknown and there are to date no studies examining the relationship between age and fT3/fT4 in low T3 syndrome.

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**Table 3** Numbers of the patients with fT3/fT4 being < or > 2 in group C and non-group C

|        | < 2 | > 2 | Total |
|--------|-----|-----|-------|
| Group C| 0   | 4   | 4     |
| Non-group C | 54 | 171 | 225   |
| Total  | 54  | 175 | 229   |

The sensitivity, specificity, positive predictive value and negative predictive value are 100%, 24%, 2.3% and 100%, respectively. # The unit of fT3 and fT4 are pg/mL and ng/dL, respectively.

**Table 4** Thyroid function in the fifth participants with central hypothyroidism above the age of two during the study periods

| Sex | Age  | Complication/MRI finding | TSH | fT3 | fT4 | fT3/fT4 | Risk factors for low T3 syndrome at samplings |
|-----|------|--------------------------|-----|-----|-----|---------|-----------------------------------------------|
| F   | 2.0  | Prader-Willi syndrome    | 7.63| 4.11| 0.89| 4.62    | None                                         |
| F   | 6.5  | Invisible pituitary stalk| 2.81| 3.54| 0.76| 4.66    | None                                         |
| F   | 6.5  | Craniopharyngioma        | 1.05| 2.90| 1.08| 2.69    | 2 weeks post-operation                      |
| F   | 7.1  | Germ cell tumor          | 1.37| 3.93| 0.51| 7.71    | None                                         |
| M   | 2.2  | Septo-Optic Dysplasia    | 3.72| 4.11| 0.88| 4.67    | None                                         |
| M   | 2.8  | Craniopharyngioma        | 0.56| 1.37| 0.26| 5.27    | None                                         |
| M   | 2.9  | Septo-Optic Dysplasia    | 1.69| 4.91| 0.75| 6.55    | None                                         |
| M   | 4.0  | None                     | 1.21| 3.50| 0.68| 5.15    | None                                         |
| M   | 4.2  | Invisible pituitary stalk| 1.96| 4.75| 0.81| 5.86    | None                                         |
| M   | 5.3  | Adenophysitis            | 0.54| 2.14| 0.84| 2.55    | Diabetes insipidus (not treated)              |

The unit of fT3 and fT4 are pg/mL and ng/dL, respectively.
The method of analysis employed in our study design was unique. The cut-off value of 2.0, determined by using the first clinically defined set of patients, i.e., groups A and CH, was validated using the second, biochemically defined set of patients, i.e., groups L and C. This second step in validation was done with more than 200 data. With regard to low T3 syndrome (group L) in comparison with central hypothyroidism (group C), the validation benefited from a large subject pool. The third step in validation in central hypothyroidism was performed by using the different cohort, the ten participants described as the fourth set of the participants in the subject session of this manuscript.

There are at least three limitations to this study. First, the number of patients in group C was small. Thus we tried to overcome this issue by adding the 10 patients from the two other institutions, constituting the fourth set of participants in this study. Second, reverse T3 was not measured in this study due to the unavailability of current reverse T3 measurements in Japan for the past ten years. Third, adult subjects were not included, leaving open the possibility that the cut-off value may be different for the elderly, an issue that should be addressed in a future study.

The cut-off value, which excludes central hypothyroidism without the complication of low T3 syndrome, might be higher than 2.0. Some patients with suspected central hypothyroidism might suffer complications involving low T3 syndrome. This was observed in the results of fourth set of the patients (see Table 4). It is known that patients with combined pituitary hormone deficiencies, who possibly also suffer from central hypothyroidism, may experience appetite and weight loss, risk factors for low T3 syndrome.

It remains to be seen whether this cut-off value can be interpreted as indicating a fT3/fT4 above the cut-off value for the initiation of the treatment even in suspected cases of low T3 syndrome. Many endocrinologists assume that low T3 syndrome reflects a beneficial and physiological response, but this assumption is not evidence-based. Indeed, there have been at least two reports suggesting that the lower the fT4 value is, the worse the prognosis [11, 12]. The fT3/fT4 theoretically increases in patients with a severe type of low T3 syndrome in which low T3 levels are accompanied with low T4 levels.

In conclusion, an fT3/fT4 less than 2.0 suggests low T3 syndrome rather than central hypothyroidism for patients from the age of two to eighteen years. The importance of fT3/fT4 in the differential diagnosis of central hypothyroidism and low T3 syndrome should be further verified in the future.

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### Disclosure Statement

The authors have nothing to disclose.

### Supplementary Table 1

| Height (X) | d | a | b | c | Standard body weight (Y) |
|-----------|---|---|---|---|--------------------------|
| 101≤X<140 | 3.03882E-05 | -0.00571495 | 0.508124 | -9.17791 | Y=dX³+aX²+bX+c |
| 140≤X<149 | -0.000085013 | 0.0370692 | -4.6558 | 191.847 |
| 149≤X<184 | -0.000310205 | 0.151159 | -23.6303 | 1231.04 |
| 101≤X<140 | 0.000127719 | -0.0414712 | 4.8575 | -184.492 | Y=dX³+aX²+bX+c |
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**Nomura et al.**

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### Supplementary Table 2  Body weight (kg) and BMI corresponding to -20% of obesity index for each sex and height

| Height (cm) | Standard body weight (kg) | Body weight when obesity index was -20% (kg) | BMI when obesity index was -20% (kg·m⁻²) |
|------------|---------------------------|---------------------------------------------|------------------------------------------|
| 110        | 18.01                     | 14.41                                       | 11.91                                    |
| 120        | 22.01                     | 17.61                                       | 12.23                                    |
| 130        | 27.06                     | 21.65                                       | 12.81                                    |
| 140        | 33.32                     | 26.65                                       | 13.60                                    |
| 150        | 40.63                     | 32.5                                        | 14.44                                    |
| 160        | 49.26                     | 39.41                                       | 15.39                                    |
| 170        | 58.35                     | 46.68                                       | 16.15                                    |
| 180        | 66.02                     | 52.82                                       | 16.30                                    |

### Supplementary Table 3  Transformation of Roche kits (X) into Fukurebio kits (Y)

| Values of Fujirebio Kits | Conversion formula for the transformation |
|--------------------------|------------------------------------------|
| TSH (Y)                  | = 0.7695 X + 0.2258                       |
| fT3 (Y)                  | = 1.03564 X + 0.3496                      |
| fT4 (Y)                  | = 0.9993 X - 0.1525                       |