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Original Article

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Clinical Characteristics of Failure to Thrive in Infant and Toddler: Organic vs. Nonorganic

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Purpose: To investigate the clinical characteristics and outcomes among infants and toddlers with failure to thrive (FTT).

Methods: This retrospective study was done with 123 patients who had visited Pusan National University Children's Hospital during their first two years of life and had received an FTT diagnosis. We compared the clinical characteristics of the patients based on the causes of their FTT and their ages at the time of first hospital visit. We investigated triggering factors, feeding practices, and outcomes in 25 patients with nonorganic FTT (NOFTT).

Results: Eighty cases (65.0%) were NOFTT. The gestational ages, birth weights, and weights at the first visits were significantly lower in patients with organic FTT (OFTT) ($p < 0.05$). Infants who had first visited the clinic at age < 6 months had the least z-score. The percentage of patients with severe weight decline was higher in OFTT than in NOFTT (60.0% vs. 17.3%). The z-scores at the follow-up visits were improved after treatment in both of the groups. Preceding infection was the most common triggering factor of NOFTT and persecutory feeding as abnormal behavior of caregiver was observed in 22 cases (88.0%). After treatment with feeding method modification, all patients with NOFTT showed normal growth.

Conclusion: Weight decline is more severe in OFTT patients and in younger patients at the first visit. Infants with FTT can attain normal weight gain growth by treating organic diseases and supplying proper nutrition in OFTT, and by correcting abnormal dietary behavior of caregiver in NOFTT.

Key Words: Failure to thrive, Infant

INTRODUCTION

Failure to thrive (FTT), a term that refers to infants and toddlers whose weights or weight gaining rates are strikingly lower than expected from children of the same ages, genders, and ethnicities, is used for cases where there are no effects on the height and head circumference or just slight influence is found despite underweight. It appears mainly in 1-2 year old children but can occur at any moment in one's

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childhood. Data about its prevalence are not sufficient and it varies with diagnostic criteria and subject populations. In the case of the USA, 5-10% of children in primary care settings, and 3-5% of children in hospital care settings have been reported to fall within this category [1].

Currently, there is no established consensus about anthropometric standards for diagnosing FTT [2,3]. Three criteria for weight are used for the diagnosis. A child under the age of 2 can be determined as having FTT when his or her weight for age is under the 3 or 5 percentile at least once, his or her weight is under 80% of the ideal weight for his or her age, and he or she loses weight across 2 major percentile lines in a standard growth table that uses the 5, 10, 25, 50, 75, 90 percentiles as major percentiles [4].

Though it occurs for various reasons, most FTT cases are due to insufficient nutritional intake for behavioral or psycho-social factors [5]. It is classified into organic FTT (OFTT) and nonorganic FTT (NOFTT) based on the presence and absence of underlying conditions that can trigger growth restriction, but there are many cases where the two are mixed [5,6]. Studies vary in reporting OFTT ranging 15-58% [7-9].

Moon et al. [10] investigated 74 patients aged 1 month-13 years to report that intrauterine growth restriction and familial short stature were main causes in patients under the age of 3 and familial short stature and constitutional growth restriction in patients aged 3 or older, and that their average calorie intakes was 76.2% of the recommended amount. Lee et al. [11] investigated etiologic diseases in 83 children under the age of 2 who had not gain weight for current 2 weeks to conclude that gastrointestinal milk allergy, milk protein induced enterocolitis, gastroesophageal reflux etc. were main causes. Nam et al. [12] and Lim and Kim [13] explored the anthropometric measurements of 80 FTT children at the age of 2 and at the age of 3 and the causes of their FTT, and claimed that OFTT was the cause in about 80% of the patients.

Lee's study [14] investigated the differences between healthy children and 25 NOFTT patients along with their mothers. The conclusion is that the NOFTT cases occurred complicatedly due to the patients' particular characters and low appetites and their mothers' lack of skills and knowledge in nutrition rather than their psychopathology.

Early detection and treatment of FTT is very important because it can result in disorders not only in physical growth but also in cognitive and behavioral development, and appropriate treatment can prevent long term complications [15-18]. However, most of the literature just emphasize in principle that appropriate calorie supply is the most important in the treatment of FTT, but overlook the reasons of low calorie intake observed in NOFTT patients who account for the majority of FTT patients. Tube feeding in the child who does not grow well and refuse to eat can be considered if no cause is found and other therapies fail. However, this can reinforce to feed [19].

We have no domestic reports so far that compared and analyzed the clinical differences between OFTT and NOFTT cases and their time of first visiting, and addressed triggering factors and treatment responses of NOFTT. In particular, there has been only one paper [14] on NOFTT patients who account for the majority of outpatients. Thus, the authors took as the subjects of this study, patients with FTT visiting the Clinic for Pediatric Gastroenterology and Nutrition at Pusan National University Children's Hospital to compare their clinical differences according to the causes of FTT and their time of first visiting, and in particular, take a look at the triggering factors of NOFTT and their treatments results.

MATERIALS AND METHODS

We carried out a retrospective study with 123 infants and toddlers under the age of 24 months who visited the Outpatient Clinic for Pediatric Gastroenterology and Nutrition at Pusan National University Children's Hospital from November 2008 to May 2013 for the reason that they did not gain weight well. A patient with FTT is defined as one whose weight or height for age is under the 5 percentile (z-score <-1.645) or whose height for weight is un-

der the 10 percentile (z-score <-1.281). We used the percentiles in the 2007 Korean Children and Adolescents Growth Standard [20]. Patients with low weight due to short stature, and patients in weight controlling for normal weight restoration from overweight were excluded. We recognized significant weight gaining for age as normal growth.

For patients with FTT diagnosis, we judged whether there were underlying diseases by hearing their medical histories including their birth and accompanied conditions and conducting physical examinations. Also, we determined their nutritional statuses including the presence or absence of iron deficiency anemia by conducting general blood tests including total protein, albumin, white blood cells, total lymphocytes, and hemoglobin, and made detailed questions about the types, amounts, and frequencies of their daily diets, based on which we evaluated the adequacy of their currently provided nutrition. We arranged appropriate nutritional supplies in parallel with the treatment of underlying diseases when OFTT was determined, while we analyzed triggering factors and the caregivers' feeding behavior to educate them to improve their problems when NOFTT was determined. Then, we followed up and observed them every week or every two weeks. That is to say, we did not force patients rejecting milk-feeding to eat, lengthened milk-breeding intervals when they were short, inhibited feeding during sleeping, and encouraged patients resisting weaning foods to change their diets into weaning foods. In follow-up, we checked their dietary diaries for evaluating their calorie intake, and re-evaluated the extents of their growth by measuring their heights, weights, and head circumferences.

We analyzed whether there were differences in anthropometric measurements and blood test results between OFTT and NOFTT patients, and compared their weights at birth, at hospital visiting, and at follow-up observation within less than 6 months to evaluate their weight gaining. Also, as for NOFTT cases, we investigated triggering factors, onset ages, abnormal dietary behavior, treatment methods, and treatment responses. The patients were classified into three groups based on their ages at first hospital visit (younger than 6 months, 7-12 months old, and 13-24 months old) to analyze whether there were differences in anthropometric measurements and blood test results, and then compared their weights at birth, at hospital visit, and at follow-up observation within less than 6 months to evaluate their weight gaining. We used z-score to compare the patients' anthropometric indices of height, weight, and head circumference. In order to evaluate severity of FTT, we arbitrarily classified into grade as follow: $-2.0 \leq$ z-score <-1.645 is mild, $-3.0 \leq$ z-score <-2.0 is moderate and z-score <-3.0 is severe.

The results of their examination at hospital visit were analyzed in descriptive statistics, and paired t-test was conducted for the comparison of the differences at birth, at hospital visit, and at follow-up observation. Independent t-test and ANOVA were performed to compare the groups. The IBM SPSS Statistics program version 21.0 (IBM Co., Armonk, NY, USA) was used to carry out the statistical analysis, and statistical significance was recognized when $p<0.05$.

RESULTS

The number of females out of a total of 123 subjects was 66 (53.7%). As for the history of birth, the gestational age was 38.7±2.5, the weight at birth 2.77±0.58 kg, the height 46.5±3.09 cm, and the head circumference 32.2±2.09 cm. Ninety subjects (73.2%) were adequate for gestational age, 21 (17.1%) were small for gestational age, 108 (87.8%) were born as full-term. The age at the first hospital visit was 11.2±6.7 months.

Eighty subjects (65.0%) were NOFTT patients and 43 (35.0%) OFTT patients. As for organic causes, gastroenterologic disorder cases were 14, which accounted for the majority (11.4%). In turn, cardiac disease cases (6.5%), premature infant/intrauterine growth restriction cases (5.7%), neurodevelopmental disorder cases (4.1%), endocrinologic disorder cases (2.5%), and genetic disorder cases (1.6%) occupied the next portions in that order. The gastro-

Table 1. Comparison of Clinical Characteristics of the Patients Classified by Causes of Failure to Thrive

Characteristic	NOFTT	OFTT	*p*-value
Sex (male : female)	34 : 46 (80)	23 : 20 (43)	0.124
Gestational age (week)	39.30±1.80 (72)	37.90±3.00 (41)	<0.001
Birth weight (kg)	2.85±0.51 (72)	2.63±0.67 (41)	<0.009
First visit data (z-score)			
Body weight	−2.36±0.84 (80)	−3.33±1.41 (43)	<0.001
Height	−1.51±1.37 (54)	−2.46±1.74 (37)	0.005
Follow up visit			
Body weight (z-score)	−2.17±0.98 (28)	−3.19±2.25 (30)	0.098
Severity of FTT			
Mild	−1.43±0.87 (21)	−1.37±0.72 (7)	0.861
Moderate	−2.46±0.27 (46)	−2.56±0.30 (12)	0.283
Severe	−3.47±0.52 (13)	−4.28±1.01 (24)	0.003
Laboratory findings			
Protein (g/dL)	6.67±0.58	6.46±0.94	0.185
Albumin (g/dL)	4.36±0.29	4.14±0.54	0.016
White blood cell (/mm^3)	10,713±3,501	10,932±4,275	0.962
Hemoglobin (g/dL)	11.90±1.10	11.56±1.66	0.268
Lymphocyte (/mm^3)	6,243±2,142	5,399±2,209	0.025

Values are presented as mean±standard deviation (number). NOFTT: non organic failure to thrive, OFTT: organic failure to thrive, FTT: failure to thrive, severity of FTT mild: −2.0≤z-score<−1.645, severity of FTT moderate: −3.0≤z-score<−2.0, severity of FTT severe: z-score<−3.0.

enterologic disorders included esophageal stricture, gastroesophageal reflux, congenital megacolon, chronic diarrhea, and milk-protein induced enterocolitis. The genetic disorders included Noonan syndrome, 46,XX,del(10)(q26.2), the oncologic disorders were pineal tumor and atypical rhabdoid tumor, the immunodeficiency disorders included hyper IgE syndrome, and the respiratory diseases included subglottic stricture.

The OFTT patients had significantly lower gestational ages, and significantly lower weights at birth and at the first hospital visit than the NOFTT patients ($p<0.05$). Both the z-scores of the weights and heights at the first hospital visit were significantly low in OFTT cases ($p<0.05$, Table 1). Though the z-scores of the weights at follow-up observation were improved in both the two groups, significant improvement was observed from the OFTT group ($p<0.05$, Fig. 1). It was found from the investigation of severity in underweight that severe cases (z-score<−3.0) were much more in the OFTT cases than in the NOFTT cases (17.3% vs. 60.0%) ($p<0.05$). Laboratory findings showed significant differences in albumin and total lymphocytes ($p<0.05$), but they were within the normal range (Table 1).

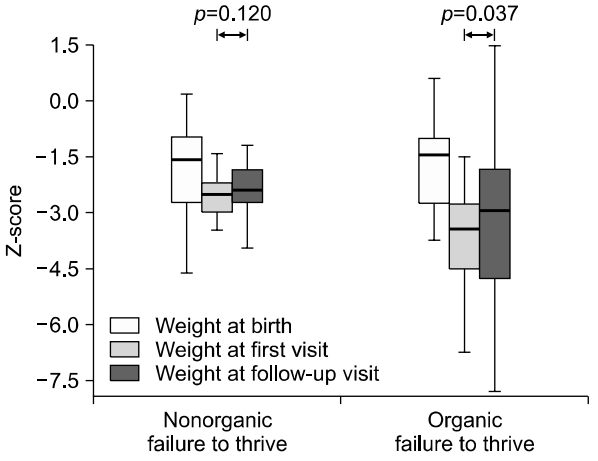

Fig. 1. Changes of z-score of weight at birth, first visit and follow-up visit in patients with organic and nonorganic failure to thrive. There was marked decline of z-score at first visit in organic failure to thrive ($p<0.001$) and improvement of z-score in both groups at follow-up visit, especially in organic failure to thrive ($p=0.037$).

We classified the patients into three groups based

Table 2. Comparison of Clinical Characteristics of the Patients Classified by Age at First Visit

	Age at first visit (month)			*p*-value
	≤6	7-12	13-24	
Sex (male : female)	13 : 21 (34)	12 : 16 (28)	32 : 29 (61)	0.383
NOFTT : OFTT	17 : 17	20 : 8	45 : 16	0.066
Gestational age (week)	39.10±1.50	37.80±3.20	39.00±2.30	0.098
Birth weight (kg)	2.82±0.57 (33)	2.58±0.64 (28)	2.84±0.54 (52)	0.111
First visit (z-score)				
Body weight	−3.22±1.13 (34)	−2.65±1.04 (28)	−2.48±1.08 (61)	0.008
Height	−2.55±2.01 (26)	−2.24±1.30 (16)	−1.45±1.28 (49)	0.011
Follow up visit Body weight (z-score)	−2.44±1.85 (22)	−2.80±1.43 (17)	−2.91±2.11 (19)	0.666
Severity of FTT				
Mild	−1.79±0.17 (8)	−0.49±1.15 (4)	1.47±0.80 (16)	0.029
Moderate	−2.63±0.187 (7)	−2.49±0.30 (17)	−2.45±0.28 (34)	0.280
Severe	−4.07±0.76 (19)	−3.85±1.04 (7)	−4.01±1.25 (11)	0.408
Laboratory findings				
Protein (g/dL)	6.13±0.63	6.48±0.99	6.90±0.46	<0.001
Albumin (g/dL)	4.00±0.40	4.26±0.56	4.44±0.22	<0.001
White blood cell (/mm^3)	11,480±4,193	11,424±3,598	10,061±3,575	0.150
Hemoglobin (g/dL)	11.14±1.85	11.90±1.36	12.14±0.86	0.007
Lymphocyte (/mm^3)	5,657±2,660	6,949±1,911	5,548±1,896	0.014

Values are presented as mean±standard deviation (number). NOFTT: non organic failure to thrive, OFTT: organic failure to thrive, FTT: failure to thrive, severity of FTT mild: −2.0≤z-score<−1.645, severity of FTT moderate: −3.0≤z-score<−2.0, severity of FTT severe: z-score<−3.0.

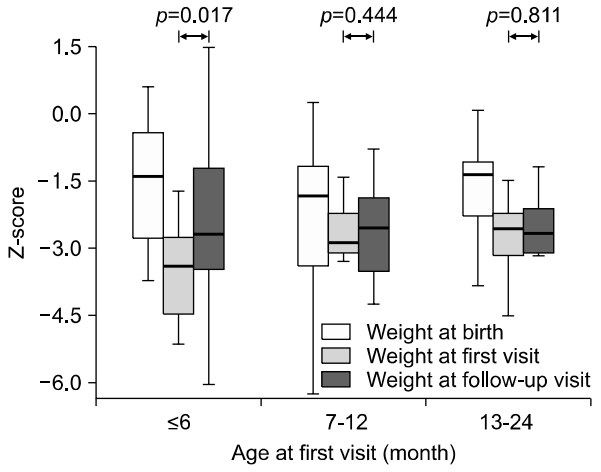

Fig. 2. Changes of z-score of weight at birth, first visit and follow-up visit according to age group. There was marked decline of z-score in the patients whose age at first visit was less than 6 months ($p<0.001$). The patients of this group showed also significant improvement of z-score at follow-up visit ($p=0.017$).

on their ages at first visit (younger than 6 months, 7-12 months old, and 13-24 months old) to compare their clinical findings. The earlier a patient's first hospital visit, the higher the chance for him or her to be an OFTT patient (50.0% vs. 37.5% vs. 26.2%) (Table 2). The z-score was the lowest in the group younger than 6 months at first visit ($p<0.05$), the number of severe patients was great, and their z-score of weights were significantly improved in follow-up ($p<0.05$). There was no evidence of significant z-score increase in the other groups (Table 2, Fig. 2).

As a result of the analysis of the 25 NOFTT patients who were possible to be subject to follow-up observation, it was found out that the average time of the onset of FTT was at the 5.7 month, and the most frequent triggering factor was preceding infection (13 subjects, 52.0%). The persecutory feeding was found from 22 caregivers (88.0%) who forced their children to eat even if they rejected feeding. For the treatment of FTT, they were encouraged to stop forcing their children to eat, lengthen milk-feeding intervals and change their diets into weaning foods if possible. In the one single case where FTT occurred as the patient with chronic nonspecific diarrhea had

Table 3. Detail Information of 25 Patients with Nonorganic Failure to Thrive

Variable	Data, n (%)
Triggering factor	
Preceding acute infection	13 (52.0)
Unknown cause	9 (36.0)
Dietary attachment of parent/caregiver	2 (8.0)
Iatrogenic	1 (4.0)
Onset of age (month)	
≤6	15 (60.0)
7-12	9 (36.0)
13-24	1 (4.0)
Feeding practice	
Persecutory	22 (88.0)
Nocturnal	2 (8.0)
Restriction	1 (4.0)
Treatment	
Not-forced feeding[a]	7 (28.0)
Increase of dietary time interval[b]	6 (24.0)
Change of dietary time[c]	2 (8.0)
Change to weaning food based diet[d]	2 (8.0)
Supply of high calorie	1 (4.0)
Normal diet	1 (4.0)
Refuse to medical advice	1 (4.0)
More than 2 methods of treatment*	5 (20.0)
Response (month)	
≤1	20 (80.0)
2-3	3 (12.0)
4-6	1 (4.0)
No response	1 (4.0)

*a+b 3 cases; b+c 1 case; c+d 1 case.

been subject to dietary restriction, the patient showed normal growth after led to normal diet without dietary restriction. Every subject except one who rejected the doctors' recommendation showed normal growth. As for treatment responses, 20 subjects (80.0%) showed responses within a month (Table 3).

DISCUSSION

Generally, cases where a child has a weight under the 5 percentile, or he or she loses weight across 2 major percentile curves are defined as FTT. However, in the case of severe FTT, as the patient's weight and height were placed on the bottom of the growth curve graphs, it is difficult to visually clarify severity, and it is uneasy to judge how far his or her condition is improved in follow-up. Thus, there have been several studies that tried to approach the issue by classifying the degrees of severity [21,22], and this study also used z-score to compare severity degrees.

The result of this study that 65% of the subjects were NOFTT patients contrasts with the existing domestic studies [12,13] reporting that OFTT patients accounted for the majority. Gastroenterologic disorders accounted for 11.4% of the causes of OFTT, and cardiac diseases 6.5%. While in Lee et al.'s study [11], gastroenterologic disorders accounted for 97.7% of the patients, another study that analyzed patients visiting a pediatric endocrine clinic [23] reported that endocrine conditions (28.9%) occupied a greater portion than gastroenterologic disorders (15.5%). The reason why the number of congenital cardiac patients was great in this study seems to be that there were many patients undergoing cardiac surgery due to the characteristics of our hospital. Thus, it is possible to know that there are many differences in the result of study based on the study populations.

Research results about the onset of FTT vary in that Moon et al. [10] reported it was the 8 month, Olsen et al. [24] the 8.3 month, and Daniel et al. [23] the 18.7 month. The average time of the patients' first hospital visit in this study was the 11.2 month, and the average time of the onset of FTT in the NOFTT patients was the 5.7 month. The possibility of early manifestation of FTT is high with OFTT as OFTT is much related with congenital conditions, while the onset of FTT could be relatively belated with NOFTT as NOFTT occurs when some special triggering factors are added in the course of normal growth. In this study, the onset of NOFTT in the subjects tended to occur in the middle infanthood as it was deeply related with preceding infection. McDougall et al.'s study [25] claims that evaluation of growth at 6-8 weeks of age is necessary because infants whose early weight gain is slow can frequently have feeding problems than controls and be related to developmental delay.

In this study, OFTT patients had more significantly low gestational ages, and weights at birth and at first visit than NOFTT patients. Also, the z-scores of

their weights at first visit and heights were significantly lower, and the number of severe patients (z-score<-3.0) were a lot greater in the OFTT patients. That is to say, the OFTT patients showed differences in growth from their birth, and had severe growth retardation when they visited the hospital. However, the z-score of weight was improved in both the groups after the treatment of FTT, but significant improvement was seen from the OFTT group. Such differences are believed to result from more positive nutritional treatment in addition to the treatment of organic diseases in the OFTT patients.

When the whole patients were compared in their time of first visit, the rate of OFTT patients were higher and the z-scores of their weights were lower as their time of first visit was earlier. Also, the number of severe patients was the greatest in the OFTT group, and significant improvement was observed in follow-up. This also suggests that the possibility of organic causes is higher and the degree of FTT is more severe in younger patients. The result of this study that rapid improvement is expected when a patient visits a hospital earlier to receive appropriate nutritional treatment and education is the same as other studies' [18,26,27] conclusions. Schmitt and Mauro's study [28] reported that patients showed faster weight gaining within 6-8 months after treatment, and they recommended that infants be subject to follow-up observation while receiving weight measurement every week and in the case of older infants, at intervals 2 weeks.

As a result of the analysis of the 25 NOFTT patients, it was found out that half the patients had preceding infection and mainly acute gastroenteritis or upper respiratory infection was the cause. It was conjectured that NOFTT was induced by those caregivers who did not understand their children's transient low appetite due to such infections and insisted their old milk-feeding methods to make their children dislike food intake. Caregivers' insistence on forcing patients who won't eat to take foods in was observed in 88% of the cases. That is to say, infants dislike food intake due to caregivers' abnormal feeding practices. Long lasting these patterns lead to NOFTT. Levy et al. [19] reported that food refusal, head turning, anticipatory gagging, meal-related gagging etc. were significantly observed from NOFTT patients, and that abnormal parental feeding practices including nocturnal feeding, forcing feeding, persecutory feeding, mechanistic feeding, prolonged feeding, conditional distraction etc. were significantly frequent in NOFTT cases. Meanwhile, there was one case where FTT occurred due to the restriction on a chronic nonspecific diarrhea patient's diet, which suggests attention to iatrogenic FTT.

As for FTT treatment, the OFTT patients recommended to receive treatment of their underlying diseases and appropriate nutritional supply, and the NOFTT patients were led to improve their dietary methods. That is to say, treatment response was showed by dietary methods modification only without using milk additives or special formula. This result shows that one can lead a patient to normal growth in a short time period without any unnecessary tests or special therapies by analyzing and correcting inducing factors and feeding behavior in terms of thorough hearing of medical history from NOFTT patients including their diet diaries.

In papers reported domestic FTT cases [10-14], the span of the ages of the patients were wide, patients without growth in a short period of time were included, the rate of OFTT patients were high, and patients with low weights due to short heights were included. In comparison, this study included infants and toddlers under the age of 2 years, and patients with low weight due to short stature were excluded. It is also rather significant as it has higher composition of NOFTT, compared OFTT and NOFTT cases, and analyzed moments of the first hospital visit, triggering factors of NOFTT and treatment responses. However, this study was not able to get necessary information from every patient as it was a retrospective study analyzing medical records, and has limitations in follow-up observation of a sufficient number of patients as it took outpatients as its subjects. It is believed that a prospective study with a large number of patients as subjects is necessary in future.

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