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Indexes of Suspicion of Typical Cow's Milk Protein-Induced Enterocolitis

This study was performed to identify clinical factors that facilitate the diagnosis of typical cow's milk protein-induced enterocolitis (CMPIE). Data from 142 consecutive patients (aged 15 to 45 days, cow's milk formula- or cow's milk and breast milk mixed-fed) admitted due to vomiting and/or diarrhea were retrospectively analyzed. These 142 subjects were divided into three groups: the CMPIE, infection, and non-infection group. Each group was composed of 16 (11.3%), 102 (71.8%), and 24 (16.9%) patients, respectively. On admission, poor weight gain (p=0.003), hypoalbuminemia (p=0.035), peripheral leukocytosis (p=0.012), and metabolic acidosis (p=0.015) were found to be more significant in the CMPIE group than those in other two groups. In CMPIE, serum albumin levels decreased from 3.3 ±0.9 g/dL on admission to 2.6±0.3 g/dL during admission (p<0.05), and methemoglobinemia was observed in 3 patients (18.8%) (p=0.012). Multiple logistic regression analysis showed that the independent predictors of CMPIE versus the infection group were failure to gain weight (OR, 10.75 [95% CI, 1.53-66.12]) (p= 0.014) and hypoalbuminemia (OR, 9.53 [95% CI, 1.62-49.01]) (p=0.010). The early recognition of indexes of suspicion for CMPIE may be of help in the diagnosis and treatment of this disorder.

Key Words : *Cow's Milk Protein-Induced Enterocolitis; Index of Suspicion*

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INTRODUCTION

Typical cow's milk protein-induced enterocolitis (CMPIE) is a non-IgE mediated hypersensitivity disorder (1), which is associated mainly with gastrointestinal symptoms (not skin or respiratory symptoms) and has a delayed onset (2-9). The vomiting and/or diarrheal symptoms of CMPIE typically begin in the first month of life in association with a failure to thrive, metabolic acidosis, and shock (2, 3, 6, 7). Therefore, the differential diagnosis of CMPIE and neonatal or infantile sepsis-like illnesses or gastroenteritis is difficult (10). In this respect, clinical indexes of suspicion may helpfully allow early and safe diagnosis and treatment of CMPIE.

CMPIE is a diagnosis that is generally made clinically (2-8). Food-specific IgE tests, e.g., skin prick, radio allergo sorbent test (RAST), or Uni-Cap tests are typically negative (2, 5), and the patch test has not been sufficiently evaluated in this disorder (10). Oral cow's milk challenge (OCC) remains the gold standard for the diagnosis of CMPIE (3, 4); however, because 20% of reactions after OCC in CMPIE lead to shock (2), it should always be borne in mind that OCC in CMPIE has attendant dangers due to the possibility of an overwhelming intestinal inflammation (2, 4, 6, 7, 9). Therefore, the recognition of indexes of suspicion for CMPIE is mandatory for early stabilization of general condition (e.g., the feeding of protein hydrolysate formula or exclusively breast feeding until the final diagnosis is made) and for preparing a standardized OCC to allow a safe confirmatory diagnosis of CMPIE (4, 10).

This study was performed to investigate and identify indexes of suspicion to facilitate the early recognition of CMPIE.

MATERIALS AND METHODS

Data collection

This study was performed retrospectively on a population of 142 consecutive patients who had been admitted to the pediatric ward at Dongsan Medical Center, Keimyung Uni-

versity School of Medicine between March 2003 and February 2006. The inclusion criteria were as follows: age 15 to 45 days, chief complaints of vomiting and/or diarrhea, and cow's milk formula or cow's milk and breast milk mixed feeding. During this period, 402 patients, aged 15 to 45 days, were admitted to our pediatric ward, and 210 patients had chief complaints of vomiting and/or diarrhea. Among these patients, 66 patients who had been exclusively breast-fed were excluded because CMPIE has not been known to occur in exclusively breast fed babies (2). Two patients were finally diagnosed as having CMPIE, but were excluded in the study population because they had been referred under the impression of CMPIE from the outside hospital. Hence, we analyzed 142 consecutive patients. Study procedures were approved by the Keimyung University Institutional Review Board.

Diagnosis of CMPIE

CMPIE was diagnosed using an open standardized OCC based on the diagnostic guidelines suggested by Powell (3, 4), Burks et al. (5), and Sicherer et al. (2). On admission, we regarded 26 patients as being at risk of having CMPIE based on associated descriptions (2-9, 12) and authors' personal experiences. When feeding was possible, a protein hydrolysate formula (HA®, Maeil Dairy Industry Co., Seoul, Korea) or exclusively breast milk was fed until the final diagnosis was made and laboratory work ups for electrolytes and acid-base imbalance, anemia, underlying infection, surgical conditions, metabolic disease, and immune disorder or other underlying diseases were performed and treated. When patients showed a stable general condition with good weight gain, and in the absence of any other identifiable cause, we performed a single and open standardized OCC (12) with informed parental consent. Total or partial parenteral nutrition was not adopted in any patient suspected of having CMPIE. Before OCC testing, baseline studies were performed, i.e., a stool smear test for occult blood, RBC and leukocyte counts, and blood sampling for absolute neutrophil count (ANC). An open challenge was performed using 0.15 g of cow's milk protein per kilogram of body weight in one feed, and patients were observed for 4 hr in a nothing-per-oral state. After OCC, clinical symptoms and laboratory findings were observed and evaluated, and in particular, the following five criteria were recorded: projectile vomiting >2 or more (at 1-4 hr post-OCC); lethargy with relative insensitivity to stimulation (at 1-4 hr); a bloody and/or a pus-like diarrhea (at 6-10 hr), all three of which were absent at baseline; a rise of peripheral blood ANC >3,500 cells/μL from baseline (at 6 hr) (2-5); and a stool smear test for occult blood and/or WBC, RBC >5 cells/HPF, not present by baseline stool smear testing (at 6-10 hr). Diaper rash and anal fissure were eliminated as possible blood sources. A positive challenge was defined as the presence of two or more positive results of these five criteria. According to these diagnostic criteria, was diagnosed in 16 (61.5%) patients among the 26 suspicious cases. Only one CMPIE patient was fed cow's milk and breast milk mixed on admission. After diagnosis, she was fed protein hydrolysate formula and breast milk mixed owing to the lack of exclusive breast milk feeding to induce adequate growth.

Division of subjects into three groups

The 142 study subjects were divided into three groups based on underlying etiologies, i.e., the CMPIE, infection, and non-infection groups. All the patients allocated to the infection and non-infection groups were successfully re-fed cow's milk formula, and experienced no clinical symptoms or complications during one week of subsequent observation or after discharge from hospital. Subjects were allocated to the infection group when they failed to meet the diagnosis criteria for CMPIE and were deemed to have an infectious condition based on clinical findings, e.g., febrile illness, and the following laboratory results, e.g., positive culture, pyuria, positive stool rotavirus test, and abnormal rise of serum C-reactine protein (CRP) level. Subjects were allocated to the non-infection group when they were not allocable to the CMPIE or infection groups and had no clinical evidences of infection.

Analysis of index parameters on admission

Seven index parameters for CMPIE were considered based on clinical findings that were reported to be characteristic of CMPIE (2-9, 12) and based on the authors' clinical experiences (12); daily weight gain between birth and admission (body weight on admission [g]-birth weight [g]/age [day]), serum albumin level on and during admission, peripheral blood leukocyte count, metabolic acidosis, peripheral blood eosinophil count, peripheral blood platelet count, and abnormal stool smear test. Failure to gain weight was defined as a daily weight gain <10 g. A low serum albumin level was regarded as <3.5 g/dL. Peripheral blood leukocytosis was regarded as >19,500 cells/μL, and metabolic acidosis as a serum bicarbonate level <22 mEq/L. Eosinophilia was defined as >500 cells/μL, and peripheral blood thrombocytosis as >750,000 cells/μL. An abnormal stool smear test was defined as positivity for occult blood and/or WBC, RBC >5/HPF. The results corresponding to the above seven parameters were compared in the three groups. The presence of methemoglobinemia ($\geq$15%) was also included.

Statistical methods

analysis of variance (ANOVA) with Turkey's test for all pairwise comparisons was used to compare the above-mentioned six indexes, except a stool smear test, and symptom durations between the groups. An abnormal stool smear test was analyzed by Fisher's exact test. The paired t-test was used to compare changes in serum albumin levels, and Fisher's exact

test was used to compare the methemoglobinemia presence in the three groups. Multiple logistic regression analysis was performed on the CMPIE and infection group; CMPIE presents clinically as a sepsis-like illness or gastroenteritis in neonates or in early infancy and resembles clinical findings in the infection group, which may not be difficult to differentiate from the clinical findings of the non-infection group. Also, multiple logistic regression analysis was performed in terms of the three ANOVA-identified independent risk factors; metabolic acidosis was not determined because blood gas analysis was performed only in 62 patients (60.8%) in the infection group. Statistical significance was accepted for p values of <0.05. Data were presented as mean±SD.

RESULTS

Data of the three study groups

Of the 142 study subjects, CMPIE was diagnosed in 16 patients (11.3%), and the infection and non-infection group were composed of 102 patients (71.8%) and 24 patients (16.9%), respectively. Mean ages of patients at admission of the CMPIE, infection, and non-infection groups were 27.0±8.8 (18-42), 24.7±8.7 (15-44), and 27.9±9.5 (16-44) days, respectively. Mean symptom durations before admission were 4.5±2.4 (1-9), 3.7±2.5 (1-11), and 4.7±2.7 (1-9) days, respectively, and no significant differences were observed between groups. Family history of atopy was observed in 2 (12.5%), 9 (8.8%), and 4 (16.7%) patients, respectively (Table 1).

Index of suspicion parameters for CMPIE

On admission, daily weight gain (p=0.003), serum albumin level on admission (p=0.035), peripheral blood leukocyte count (p=0.012), and metabolic acidosis (p=0.015) were more significant in the CMPIE group than in the other two groups. Peripheral blood eosinophil count, platelet count, and an abnormal stool test results were not significantly associated with CMPIE group compared with the other two groups (Table 1). Methemoglobinemia was observed in 3 patients (18.8%) in the CMPIE group, but not in the other two groups (p=0.001).

Daily weight gain

Daily weight gain in the CMPIE group was -3.7±12.2 (-32.5-13.3) g/day, and 81.2% of CMPIE group patients had a daily weight gain of <10 g. Daily weight gains in the infection and non-infection groups were 17.2±21.5 (-48.2-52.6) g (p<0.05, vs. CMPIE) and 21.2±12.7 (-7.5-36.6) g (p<0.05, vs. CMPIE), respectively, and 32.4% and 29.2%, respectively, were <10 g per day.

Serum albumin level on and during admission

The mean serum albumin level at admission in the CMPIE group was 3.3±0.9 (2.2-4.4) g/dL, and 56.3% of CMPIE patients had a level of <3.5 g/dL. The mean serum albumin levels in the infection and non-infection groups were 3.8±0.5 (3.1-4.8) g (p<0.05, vs. CMPIE) and 3.7±0.4 (3.3-4.5) g, respectively, and 16.7% and 29.2% of the patients in these groups were <3.5 g/dL. In the CMPIE group, the mean serum albumin level decreased to 2.6±0.3 (2.2-3.0) g/dL during admission (at 6.1±1.5 [4-11] days after admission) (p<0.05). In fact, at some stage after admission, all patients in the CMPIE group had an albumin levels of <3.0 g/dL.

Peripheral blood leukocyte count

The mean peripheral blood leukocyte count on admission in the CMPIE group was 18,311±4,901 (10,530-29,920) cells/

Table 1. Clinical data and indexes of suspicion of typical cow's milk protein-induced enterocolitis (CMPIE) compared with infection and non-infection group

	CMPIE group	Infection group	Non-infection group	p value*
Data of patients				
No. of patients (n=142)	16 (11.3%)	102 (71.8%)	24 (16.9%)	
Age (day)	27.0±8.8 (18-42)	24.7±8.7 (15-44)	27.9±9.5 (16-44)	
Symptom duration (day)	4.5±2.4 (1-9)	3.7±2.5 (1-11)	4.7±2.7 (1-9)	
Sex (M:F)	7 : 9	45 : 57	15 : 9	
Family history of atopy	12.5%	8.8%	16.7%	
Clinical parameters				
Daily weight gain (g/day)	-3.7±12.2	17.2±21.5†	21.2±12.7†	0.003
Serum albumin level on admission (g/dL)	3.3±0.9	3.8±0.5†	3.7±0.4	0.035
Peripheral blood leukocyte count (/μL)	18,311±4,901	12,010±5,984†	10,125±2,930†	0.012
Serum bicarbonate level (mEq/L)	15.2±6.1	18.3±5.5‡	23.4±4.6†,§,‖	0.015
Peripheral blood eosinophil count (/μL)	312±211	288±190	375±242	0.313
Peripheral blood platelet count (/μL)	634,321±210,162	532,129±200,212	472,674±117,233	0.130
Stool occult blood and/or WBC (+)	26.9%	22.4%	11.7%	0.995¶

*By ANOVA (analysis of variance); †p<0.05 (vs. CMPIE group) by Turkey's test for all pairwise comparisons; ‡No.=62; §p<0.05 (vs. Infection group) by Turkey's test for all pairwise comparisons; ‖No.=14; ¶by Fisher's exact test.

μL, and 43.8% of CMPIE patients had a leukocyte count >19,500/μL, whereas mean peripheral blood leukocyte counts in the infection and non-infection groups were 12,010±5,984 (2,520-44,100) cells/μL (p<0.05, vs. CMPIE) and 10,125±2,930 (5,790-18,590) cells/μL (p<0.05, vs. CMPIE), respectively, and 15.7% and none of patients in these groups had a mean peripheral blood leukocyte count of >19,500/μL.

Metabolic acidosis

Serum bicarbonate levels were measured in all CMPIE group patients, in 62 patients (60.8%) in the infection group and in 14 patients (58.3%) in the non-infection group. The mean serum bicarbonate level on admission in the CMPIE group was 15.2±6.1 (8.2-28.5) mEq/L, and 82.1% of these patients were <22.0 mEq/L, whereas mean serum bicarbonate levels in the infection and non-infection groups were 18.3±5.5 (7.0-24.8) mEq/L and 23.4±4.6 (15.0-30.8) mEq/L (p<0.05, vs. the CMPIE group and p<0.05, vs. the infection group), respectively, and 79.4% and 33.3%, respectively, had a mean serum bicarbonate level of <22.0 mEq/L.

Independent predictors of CMPIE versus the infection group

Multiple logistic regression analysis was performed on the CMPIE and infection group in terms of the three ANOVA-identified independent risk factors, i.e., daily weight gain, serum albumin level on admission, and peripheral blood leukocyte count. A failure to gain weight of <10 g/day (OR, 10.75 [95% CI, 1.53-66.12]) (p=0.014) and serum hypoalbuminemia <3.5 g/dL (OR, 9.53 [95% CI, 1.62-49.01]) (p=0.010) were identified as significant indexes of CMPIE.

DISCUSSION

The important aspect of this study is that 11.3% of early infants admitted for vomiting and/or diarrhea and who were fed a cow's milk formula or a mixture of cow's milk and breast milk, were ultimately diagnosed as having CMPIE, which suggests that this problem requires greater consideration during early evaluation. Moreover, early recognition of indexes of suspicion for CMPIE may help the diagnosis and treatment of this disorder and also better enable decision-making concerning the using of OCC.

It is usual for infants with CMPIE presenting with lethargy, vomiting, and diarrhea, to then undergo an evaluation for diverse infectious or non-infectious neonatal disorders. Thus, through the initial clinical profiles, it is difficult to differentially diagnose CMPIE from neonatal or infantile sepsis-like illness (such as, infection, gastroenteritis, necrotizing enterocolitis, or metabolic disorders) or non-infectious disorders (e.g., Hirschsprung's disease, gastroesophageal reflux disease, gastrointestinal bleeding, or endocrine disease) (10, 13, 14). The present study reveals that on admission, a failure to gain weight (<10 g/day) and serum hypoalbuminemia (<3.5 g/dL) are the highest indexes of suspicion for CMPIE. In addition, a rapid reduction in the serum albumin level to <3 g/dL during admission may be regarded an important diagnostic clue. Methemoglobinemia (≥15%), peripheral blood leukocytosis, and metabolic acidosis on admission may also provide supportive evidence of the presence of CMPIE.

A failure to gain weight (<10 g/day) represents a failure to thrive, and may be an important factor in the differential diagnosis, particularly in patients with/without infection. Although infectious or non-infectious diseases may result in inadequate weight gains by neonates and early infants, a failure to gain weight was found to provide the highest index of suspicion for CMPIE. We presume that poor weight gain or weight loss in CMPIE is the result of profuse vomiting, diarrhea, and a reduction in the amount fed due to general weakness or hypotension associated with the severe intestinal inflammation (2, 7, 9).

Serum hypoalbuminemia on admission and a rapid decrease in serum albumin levels during admission are also important clinical factors of CMPIE; however, their causes are unknown. Because a protein hydrolysate formula was fed to patients suspected of having CMPIE till a final diagnosis was made, total or partial parental nutrition was not undertaken in any CMPIE patient. Duodenal villous atrophy with increased TNF-α expression (9), methemoglobinemia (2, 7), and vomiting or bloody stool (2-9) have been mentioned in previous CMPIE reports. We assume that these findings reflect severe proximal small intestinal inflammation with protein-losing enteropathy. Further studies are needed to ascertain the cause of hypoalbuminemia in CMPIE.

This study shows that peripheral blood leukocyte count on admission is significantly higher in CMPIE patients. However, leukocytosis is a frequently encountered laboratory finding in neonates or early infants admitted with sepsis-like illnesses, and therefore, although the leukocyte count was found to be significantly more associated with CMPIE, its presence probably does not provide a high index of suspicion of CMPIE in terms of the differential diagnosis. Moreover, the prevalence of metabolic acidosis was not significantly different between the CMPIE and infection group; infectious conditions and gastroenteritis in neonates or early infants are frequently associated with metabolic acidosis. However, because leukocytosis and metabolic acidosis are frequently associated with CMPIE (43.8% and 82.1%, respectively), these findings in combination with other risk factors (e.g., a failure to gain weight and serum hypoalbuminemia) may be helpful for the differential diagnosis and early recognition of CMPIE.

Methemoglobinemia is a known phenomenon in patients with gastroenteritis during neonatal or early infantile period, but has also been reported in patients with food allergy-associated gastroenteritis (2, 7). In the present study, methemoglobinemia with cyanosis on admission was observed in

3 patients (18.8%) in the CMPIE group, and thus, may provide a diagnostic clue. Methemoglobinemia seems to result from increased heme oxidation caused by a nitrate elevation in the intestine due to reduced catalase activity in the presence of massive inflammation (7).

Peripheral blood eosinophil count on admission was not significantly different between the CMPIE group and the infected/non-infected groups. Moreover, peripheral blood thrombocytosis and an abnormal stool smear test on admission were common clinical findings in the CMPIE group, but again were not significantly different from those of the other two groups.

The present study suggests that indexes of suspicion for the early recognition of CMPIE are a failure to gain weight, hypoalbuminemia on admission, and a rapid reduction in serum albumin during admission. Methemoglobinemia, peripheral blood leukocytosis, and metabolic acidosis on admission are common laboratory findings of CMPIE, and may support a diagnosis in conjunction with other clinical factors. The early recognition of indexes of suspicion for CMPIE may allow a safe and stepwise approach to the diagnosis and treatment in this life-threatening disorder, namely, the early feeding of a protein hydrolysate formula to stabilize a patient's general condition followed by a standardized OCC to confirm the diagnosis.

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