

Measurement of prostaglandin metabolites is useful in diagnosis of small bowel ulcerations

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Abstract

BACKGROUND

We recently reported on a hereditary enteropathy associated with a gene encoding a prostaglandin transporter and referred to as chronic enteropathy associated with *SLCO2A1* gene (CEAS). Crohn's disease (CD) is a major differential diagnosis of CEAS, because these diseases share some clinical features. Therefore, there is a need to develop a convenient screening test to distinguish CEAS from CD.

AIM

To examine whether prostaglandin E major urinary metabolites (PGE-MUM) can serve as a biomarker to distinguish CEAS from CD.

METHODS

This was a transactional study of 20 patients with CEAS and 98 patients with CD. CEAS was diagnosed by the confirmation of homozygous or compound heterozygous mutation of *SLCO2A1*. We measured the concentration of PGE-MUM in spot urine by radioimmunoassay, and the concentration was compared between the two groups of patients. We also determined the optimal cut-off value of PGE-MUM to distinguish CEAS from CD by receiver operating characteristic (ROC) curve analysis.

RESULTS

Twenty Japanese patients with CEAS and 98 patients with CD were enrolled. PGE-MUM concentration in patients with CEAS was significantly higher than that in patients with CD (median 102.7 vs 27.9 $\mu\text{g/g} \times \text{Cre}$, $P < 0.0001$). One log unit increase in PGE-MUM contributed to 7.3 increase in the likelihood for the diagnosis of CEAS [95% confidence interval (CI) 3.2-16.7]. A logistic regression analysis revealed that the association was significant even after adjusting confounding factors (adjusted odds ratio 29.6, 95%CI 4.7-185.7). ROC curve analysis revealed the optimal PGE-MUM cut-off value for the distinction of CEAS from CD to be 48.9 $\mu\text{g/g} \times \text{Cre}$ with 95.0% sensitivity and 79.6% specificity.

CONCLUSION

PGE-MUM measurement is a convenient, non-invasive and useful test for the distinction of CEAS from CD.

Key words: Chronic enteropathy associated with *SLCO2A1* gene; Prostaglandin E major urinary metabolites; Chronic nonspecific multiple ulcers of the small intestine; Crohn's disease; Small intestine

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Core tip: Chronic enteropathy associated with *SLCO2A1* gene (CEAS) is a rare hereditary enteropathy associated with a gene encoding a prostaglandin transporter. It is sometimes difficult to distinguish CEAS from Crohn's disease (CD), because these diseases share some clinical features. We report the usefulness of prostaglandin E-major urinary metabolites (PGE-MUM) to differentiate CEAS from CD. PGE-MUM concentration was significantly higher in CEAS than in CD, and optimal cut-off value for the distinction of CEAS from CD to be 48.9 $\mu\text{g/g} \times \text{Cre}$ with sensitivity of 95.0% and specificity of 79.6%. In clinical practice, PGE-MUM measurement might be useful as a screening test for CEAS.

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INTRODUCTION

The use of capsule endoscopy and balloon-assisted endoscopy has enabled the precise observation of small bowel mucosal lesions in gastrointestinal disease pathology, such as Crohn's disease (CD), intestinal tuberculosis, and nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy^[1-5]. While characteristic endoscopic findings of small bowel inflammation have been reported, it is sometimes difficult to correctly diagnose patients by endoscopic findings alone in cases lacking characteristic features of the disease.

We previously reported an independent disease entity termed chronic nonspecific multiple ulcers of the small intestine (CNSU) characterized by multiple small intestinal ulcers of nonspecific histology^[6-9]. In addition, we recently found that CNSU is caused by recessive inheritance of the *SLCO2A1* gene and proposed a new nomenclature for this disease: Chronic enteropathy associated with *SLCO2A1* gene (CEAS)^[10]. Therefore, it is now possible to diagnose CEAS based on a combination of clinical features and genetic analysis. However, it is sometimes difficult to differentiate CEAS from CD because these diseases share clinical features such as persistent anemia and hypoproteinemia, susceptible age in puberty, and a predominance of ileal involvement. The differentiation between CEAS and CD is clinically essential to avoid ineffective therapies because patients with CEAS do not respond to treatment with corticosteroids or biologics^[7,9]. Moreover, since the patients with CEAS usually show low inflammatory markers in blood test^[11], it is a particularly important problem to distinguish CEAS from CD with low disease activity. In clinical practice, however, it is unrealistic to perform genetic screening for all patients suspected as CD or CEAS.

The *SLCO2A1* gene encodes a prostaglandin transporter that mediates the cellular uptake of prostaglandins. *SLCO2A1* is also the causative gene of primary hypertrophic osteoarthropathy (PHO)^[12-14]. An increase in urinary levels of prostaglandin E2 (PGE2) and prostaglandin E metabolites in *SLCO2A1*-deficient PHO individuals has been confirmed^[14]. PGE2 is known to have the protective effect on the mucosal injury, however it is difficult to directly measure PGE2 level in local tissues or in the blood because of its extremely rapid metabolism^[15]. Prostaglandin E-major urinary metabolite (PGE-MUM) is known to be stable and we have also previously demonstrated an increase in the urinary levels of prostaglandin E metabolites in CEAS patients^[10]. Therefore, this study investigated whether PGE-MUM are useful for differentiating CEAS from CD.

MATERIALS AND METHODS

Subjects

Among the participants of our previous studies^[10,16,17] and the patients diagnosed as CEAS or CD at Kyushu University hospital, we enrolled 20 Japanese patients with CEAS and 98 patients with CD for the present investigation. A diagnosis of CEAS was confirmed based on published clinical criteria^[18,19] with genetic analysis (Supplementary Table 1). The diagnosis of CD was based on the Japanese diagnostic criteria for CD^[20]. No patients were administered prostaglandin analogues or NSAIDs at the time of urine sample collection. All urine and blood samples were collected after obtaining written informed consent. This study was approved by the institutional review board at each collecting site in accordance with the Declaration of Helsinki Principles.

Clinical characteristics

Clinical information including age, gender, history of surgery, concomitant drugs, serum C reactive protein (CRP) levels, disease location, and disease duration was collected from each participating institution. Because the PGE2 metabolite concentration was reported to increase in cases of thiazide-induced hyponatremia^[21] and laxative sennoside administration^[22], we collected information about the use of these medications. Because the PGE-MUM concentration was reported to be influenced by age, gender, smoking habit, and pulmonary inflammatory conditions including chronic fibrosing interstitial pneumonia^[15,23], we also collected information about smoking habit and pulmonary disease. Age was determined at the time of urine sample collection. Smoking habit was defined as never, current (> 6 mo on a daily basis), and former (cessation of smoking > 6 mo). Pulmonary diseases included chronic respiratory disease, diffuse lung disease, and any other lung or airway disease. History of surgery was defined as a history of intestinal resection at the time of study enrolment. The site of involvement was determined by radiographic and/or

Table 1 Clinical characteristics of the study subjects

	CEAS (n = 20)	CD (n = 98)	P value ¹
Age, yr	56 (41-63)	44 (38-54)	0.098
Gender			
Male	5 (25)	66 (67)	0.0008
Female	15 (75)	32 (33)	
Smoking			
Never smoker	16 (80)	68 (69)	0.42
Current smoker	1 (5)	13 (13)	
Former smoker	3 (15)	17 (18)	
Pulmonary disease	1 (5)	5 (5)	1
History of surgery	13 (65)	59 (60)	0.8
CRP, g/dL	0.30 (0.11-0.53)	0.13 (0.03-0.58)	0.26
Disease location			
L1, ileal		34 (35)	
L2, colonic		14 (14)	
L3, ileocolonic		50 (51)	
Disease duration, yr	33 (19-42)	20 (13-29)	0.0055

¹Mann-Whitney *U*-test or Fisher's exact test. Data are the number (%) or median (interquartile range). Significant *P* values are indicated in bold. CEAS: Chronic enteropathy associated with *SLCO2A1* gene; CD: Crohn disease; CRP: C reactive protein.

endoscopic findings, and these patients were categorized according to the Montreal classification^[24]. Disease duration was defined as the period from the onset of symptoms until study enrolment.

Genetic analysis

We used genomic DNA samples extracted from peripheral blood in our previous studies^[10,16,17,25]. In advance, we checked and confirmed that none of the patients with CD had homozygous or compound heterozygous *SLCO2A1* mutations with regards to the major six sites in our previous report^[10], including c.421G>T, c.664G>A, c.940+1G>A, c.1372G>T, c.1461+1G>C, and c.1807C>T. The diagnosis of CEAS was confirmed with 90.2% sensitivity by genotyping these 6 mutations on the basis of our previous investigation.

Measurement of prostaglandin E major urinary metabolite concentrations

All PGE-MUM concentrations were measured at SRL Inc. (Tokyo, Japan) by using a bicyclic PGE-MUM radioimmunoassay kit (Institute of Isotopes Co., Ltd. Budapest, Hungary). PGE-MUM, 7 α -hydroxy-5, 11-diketotetranorprosta-1, 16-dioic acid derived from PGE1 and PGE2 can be transformed to bicyclic PGE-MUM by alkali treatment. Each urine sample was collected and submitted individually according to the manufacturer's protocol described by Fujiwara *et al*^[22]. The urine samples were frozen and stored at -20 °C until the assay. PGE-MUM concentrations were corrected by the urinary creatinine concentration.

Statistical analyses

Categorical variables were expressed as the number (%) and continuous variables were expressed as the median (interquartile range). Comparison of the variables between CEAS and CD were performed using the chi-squared test, Fisher's exact probability test, or the Mann-Whitney *U*-test, where appropriate. The associations between clinical factors and the PGE-MUM concentration were estimated using univariable linear regression analyses. Because of the skewed distribution of the PGE-MUM concentration, values were log-transformed and used for regression analysis.

For the analysis of the clinical significance of PGE-MUM concentration to differentiate CEAS from CD, the logistic regression model was used to estimate the odds ratios (ORs) with 95% confidence intervals (CIs). The diagnostic accuracy of PGE-MUM concentration was evaluated using the area under the curve (AUC) with the receiver operating characteristic (ROC). The optimal cut-off value of PGE-MUM concentration for the diagnosis of CEAS was determined based on the maximum Youden Index (sensitivity + specificity - 1). In addition, sensitivity and specificity were compared using several cut-off values to confirm the diagnostic accuracy of this

cut-off value. Statistical analyses were performed using JMP version 13.0 (SAS Institute, Cary, NC, United States). A *P* value of 0.05 or smaller was considered statistically significant.

RESULTS

Baseline patient characteristics

The enrolled subjects consisted of 20 patients with CEAS (CEAS group) and 98 patients with CD (CD group). The clinical characteristics of the patients are shown in [Table 1](#). In the CEAS group, female patients were more frequent compared with the CD group. The disease duration was significantly longer in the CEAS group than in the CD group (median 33 *vs* 20 years, *P* = 0.0055). There was no significant difference in smoking status or medical history of pulmonary disease. Because most patients with CD were in clinical remission at the time of urine sample collection, the CRP levels remained low in the CD group.

PGE-MUM concentrations

Overall, 118 urinary samples were obtained from CEAS and CD patients. The PGE-MUM concentration ranged from 7.7 to 402.0 (median 34.1) $\mu\text{g/g} \times \text{Cre}$. [Table 2](#) shows the result of univariable linear regression analysis. A positive history of pulmonary disease and history of surgery were significantly associated with a higher PGE-MUM concentration (*P* < 0.0001 and *P* = 0.029, respectively). Serum CRP value was marginally associated with PGE-MUM concentration (*P* = 0.078). Factors with a *P* value < 0.1 were included in the multivariate analysis considering the possibility of confounding factors.

The PGE-MUM concentration was significantly higher in the CEAS group than in the CD group [median interquartile range (IQR): 102.7 (62.0-155.0) $\mu\text{g/g} \times \text{Cre}$ *vs* 27.9 (19.6-40.0) $\mu\text{g/g} \times \text{Cre}$, *P* < 0.0001, [Figure 1](#)]. Crude OR of 1 log unit increase in the PGE-MUM concentration for the distinction between CEAS and CD was 7.3 (95%CI 3.2-16.7, [Table 3](#)). This prediction model showed good differentiating ability between CEAS and CD, with an AUC of 0.90 (95%CI 0.82-0.95). This association was significant even after adjusting for possible confounding factors including age, gender, medical history of pulmonary disease, history of surgery, disease duration, and serum CRP value (model 3). The multivariate-adjusted OR was 29.6 (95%CI 4.7-185.7), with an AUC of 0.95 (95%CI 0.86-0.98).

Correlation between PGE-MUM and CD phenotype

The PGE-MUM concentration in the colonic CD group (L2) was significantly lower than in the other groups (median: 16.5 $\mu\text{g/g} \times \text{Cre}$ *vs* 29.5 $\mu\text{g/g} \times \text{Cre}$, *P* = 0.036), and the PGE-MUM concentration of the ileal CD group (L1) was significantly higher than in the colonic CD group (median: 32.9 $\mu\text{g/g} \times \text{Cre}$ *vs* 16.5 $\mu\text{g/g} \times \text{Cre}$, *P* = 0.017). When we confined the subjects to those with ileal CD, the PGE-MUM concentration in the CEAS group was still significantly higher than that in the ileal CD group (median 102.7 $\mu\text{g/g} \times \text{Cre}$ *vs* 32.9 $\mu\text{g/g} \times \text{Cre}$, *P* < 0.0001).

PGE-MUM cut-off level

[Figure 2](#) shows the ROC curve of the PGE-MUM concentration to differentiate CEAS from CD. Based on the ROC analysis, the optimal cut-off value was identified as 48.9 $\mu\text{g/g} \times \text{Cre}$, which differentiated CEAS from CD with 95.0% sensitivity and 79.6% specificity ([Supplementary Table 2](#)). The AUC was 0.90 (95%CI, 0.82-0.95).

Genetic screening in CD patients with a high PGE-MUM concentration

Among the CD group, six patients had particularly high PGE-MUM concentrations (> 100 $\mu\text{g/g} \times \text{Cre}$). Although we confirmed that they did not harbor the six major mutations in the *SLCO2A1* gene, we screened all 14 coding exons and intron-exon boundaries of the *SLCO2A1* gene using Sanger sequencing to exclude a possible misdiagnosis of CEAS. No homozygous or compound heterozygous *SLCO2A1* mutations were found in the six CD patients.

DISCUSSION

CEAS was initially reported as a novel disease entity referred to as "C" in the Japanese literature in the 1960s^[26]. We recently reported it is an autosomal recessive inherited disease^[8] caused by loss-of-function mutations in the *SLCO2A1* gene^[10]. Small bowel lesions in CEAS are characterized by multiple shallow ulcers with a circular or

Table 2 Factors associated with prostaglandin E major urinary metabolite concentrations

	Univariable linear regression (<i>P</i> value)
Age	<i>P</i> = 0.47 (0.067)
Gender (1, female; 0, male)	<i>P</i> = 0.26 (0.10)
Smoking (1, Current or former smoker; 0, Never smoker)	<i>P</i> = 0.17 (-0.13)
Pulmonary disease	<i>P</i> < 0.0001 (0.36)
History of surgery	<i>P</i> = 0.029 (0.20)
CRP	<i>P</i> = 0.078 (0.16)
Disease duration	<i>P</i> = 0.0040 (0.26)

The values of prostaglandin E major urinary metabolite were log-transformed. Significant *P* values are indicated in bold. CRP: C reactive protein.

eccentric oblique configuration^[18]. In contrast, CD typically develops longitudinal ulcers and cobblestoning, and ulcerations are predominantly located on the mesenteric side. However, both CEAS and CD involve the ileum with occasional ileal stenoses, and the clinical features of CEAS and CD are similar; therefore, it is not easy to differentiate CEAS from CD based on clinical manifestations alone^[11]. Although immunohistochemical staining for SLCO2A1 protein in biopsy specimens from the GI tract was reported to be useful to distinguish CEAS from CD^[27,28], a more convenient and non-invasive screening test is required.

PGE-MUM, a major urinary metabolite derived from PGE2, is clinically used to assess the severity of inflammatory conditions such as interstitial pneumonia^[23], cystic fibrosis^[29], and ulcerative colitis^[30,31]. Similarly, urinary PGE2 metabolite concentrations in patients with CD are higher than those in patients with colorectal neoplasms and healthy controls^[32]. Indeed, PGE-MUM concentrations in patients with CD (median 27.9, IQR 19.6-40.0 µg/g × Cre) in the present study were higher than those in Japanese healthy controls (median 13.1, IQR 10.3-17.2 µg/g × Cre) as reported in previous studies^[15,23]. Nevertheless, the PGE-MUM concentration, a surrogate marker of physiological PGE2 levels^[30], in patients with CEAS was significantly higher than in patients with CD. This difference was still significant even after the adjustment for confounding factors. In addition, we demonstrated that the provisional cut-off value (48.9 µg/g × Cre) of PGE-MUM had a differentiating ability with 95.0% sensitivity and 79.6% specificity (AUC 0.90). Therefore, PGE-MUM is useful to distinguish CEAS from CD.

Although prostaglandins are mediators of active inflammation, many experimental studies have indicated that they play pivotal roles in maintaining mucosal homeostasis^[33] and mucosal repair^[34] of the intestine. PGE2 is mainly derived from arachidonic acid by cyclooxygenase and PGE synthase and PGE2 acts through four different receptor subtypes (EP1, EP2, EP3 and EP4), which partly determines the various physiological effects of PGE2 including the regulation of acid secretion, bicarbonate secretion, mucus production, and mucosal blood flow^[35]. In particular, dimethyl PGE2 (dmPGE2), a stable derivative of PGE2, was reported to exert a potent inhibitory effect against indomethacin-induced intestinal injuries in a rat model *via* activation of EP3 and EP4 receptors^[36]. It was also shown that the deleterious effect of indomethacin on the healing of intestinal ulcers was induced by an EP4 antagonist and suppressed by the co-administration of PGE2 as well as an EP4 agonist^[34]. These results indicate that the protective effect of PGE2 on mucosal injury of the intestine is caused by EP3 and EP4 activation.

PHO, which develops skin and bone disorders caused by impaired prostaglandin metabolism, is classified into two types: PHOAR2 caused by the *SLCO2A1* gene^[12], and PHOAR1 caused by the *HPGD* gene^[37]. Prostaglandin-signaling is terminated by the cellular uptake of prostaglandins *via* the prostaglandin transporter, followed by intracellular oxidation by 15-ketoprostaglandin dehydrogenase (15-PGDH) encoded by the *HPGD* gene^[38]. Thus, cellular uptake of prostaglandins is the first critical step in inactivating prostaglandins. The *SLCO2A1* gene mediates the degradation of prostaglandins *via* their intracellular uptake^[39,40]. The *HPGD* gene is also related to the degradation of prostaglandins by encoding intracellular oxidation enzymes of 15-PGDH. In both conditions, significantly elevated plasma PGE2 levels have been observed^[13,37]. Because PGE2 promotes the proliferation of osteoblasts in bone tissue *via* the expression of vascular endothelial growth factor^[41,42], various clinical manifestations of PHO such as digital clubbing, periostosis, acroosteolysis, painful joint enlargement, and thickened skin, are suggested to be the consequence of an

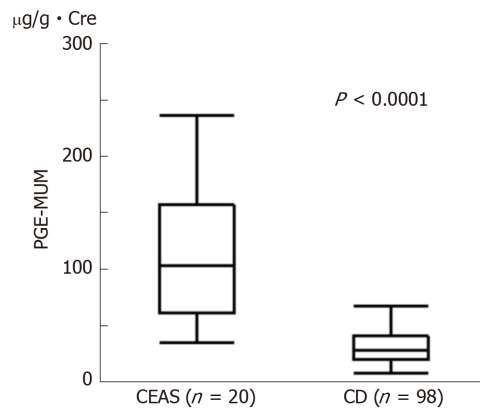


Figure 1 Comparison of Prostaglandin E-major urinary metabolites concentrations between chronic enteropathy associated with *SLCO2A1* gene ($n = 20$) and Crohn's disease ($n = 98$) groups. Prostaglandin E-major urinary metabolite concentrations in the chronic enteropathy associated with *SLCO2A1* gene group were significantly higher than those in the Crohn's disease group [median (interquartile range): 102.7 (62.0-155.0) $\mu\text{g/g} \times \text{Cre}$ vs 27.9 (19.6-40.0) $\mu\text{g/g} \times \text{Cre}$, $P < 0.0001$]. Mann-Whitney *U*-test. CEAS: Chronic enteropathy associated with *SLCO2A1* gene; CD: Crohn's disease; PEG-MUM: Prostaglandin E-major urinary metabolite.

overabundance of PGE2. Although PGE2 is protective against gastrointestinal mucosal injuries^[35,42], multiple ileal ulcers occur in patients with CEAS, in whom systemic levels of PGE2 are elevated. Considering our previous result that the prostaglandin transporter was expressed on the cellular membrane of vascular endothelial cells^[10], it can be presumed that impaired prostaglandin use in the intestinal mucosa caused by mutation of the *SLCO2A1* gene is a major factor in the pathogenesis of intestinal ulcers in CEAS.

Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is another disease entity that causes gastrointestinal ulcerations resembling CEAS^[43,44]. Recently, recessive mutations in the *PLA2G4A* gene, encoding cytoplasmic phospholipase A2- α (cPLA2 α), which hydrolyses cellular membrane phospholipids into arachidonic acids, have been identified as a cause of CMUSE^[44,45]. Because the loss-of-function of cPLA2 α decreases systemic levels of PGE2 (approximated by PGE-MUM) and thromboxane A2^[45], multiple small bowel ulcers, as well as the dysfunction of platelet aggregation are observed in patients with CMUSE^[46]. Although precise analyses of the morphologic features of gastrointestinal lesions in CMUSE have not been reported yet, it seems likely that CEAS and CMUSE share morphologic features regarding the gastrointestinal lesions. In this sense, the measurement of PGE-MUM concentrations can be assumed to be useful to differentiate CEAS from CMUSE, although genetic testing is mandatory to confirm the diagnosis.

This study had several limitations. First, the sample size of the patients with CEAS was relatively small because CEAS is a rare disease. Therefore, we could not validate the cut-off value for the distinction between the two diseases. Second, because most of our CD patients were in clinical remission, the cut-off value may not be appropriate for the distinction of CEAS from active CD. Indeed, some patients with quiescent CD had markedly high PGE-MUM concentrations. Third, we could not completely rule out the possibility that the patients with CD had recessive mutations in the *SLCO2A1* gene. Although we checked the major six mutations of the *SLCO2A1* gene in patients with CD, 9.8% of the mutations might be overlooked based on our previous result^[10].

In conclusion, the measurement of PGE-MUM might be a convenient, non-invasive and useful test to differentiate CEAS from CD, although genetic analysis is mandatory for the confirmation of CEAS. Further studies are necessary to clarify the pathogenesis of CEAS to explore therapeutic targets of this disease.

Table 3 Convert odds ratio for prostaglandin E major urinary metabolite

	Model 1	Model 2	Model 3
Odds ratio of 1 log unit change	7.3	6	29.6
(95%CI)	(3.2-16.7)	(2.6-13.9)	(4.7-185.7)
AUC (95%CI)	0.90 (0.82-0.94)	0.93 (0.87-0.96)	0.95 (0.86-0.98)

CI: Confidence interval; AUC: Area under the curve; Model 1: Prostaglandin E-major urinary metabolite; Model 2: Prostaglandin E-major urinary metabolite + Age + Gender; Model 3: Prostaglandin E-major urinary metabolite + Age + Gender + Medical history of pulmonary disease + History of surgery + Disease duration+ C reactive protein.

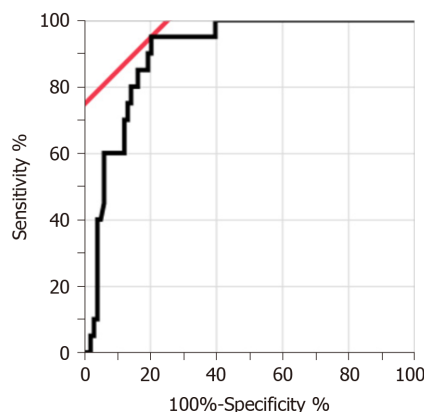


Figure 2 Receiver operating characteristic curve of Prostaglandin E-major urinary metabolites concentrations for differentiation between chronic enteropathy associated with *SLCO2A1* gene and Crohn's disease. The area under the receiver operating characteristic curve was 0.90 (95% confidence interval, 0.82-0.95). The optimal cut-off value was 48.9 $\mu\text{g/g} \times \text{Cre}$.

ARTICLE HIGHLIGHTS

Research background

Chronic enteropathy associated with *SLCO2A1* gene (CEAS) is a rare small intestinal disease, but distinct clinical condition from Crohn's disease (CD). To date, we can make a correct diagnosis of CEAS by combination of clinical features and genetic analysis. However, CEAS is sometimes misdiagnosed as CD, because these diseases have some clinical features in common.

Research motivation

A more convenient and non-invasive screening test will help to diagnose CEAS correctly.

Research objectives

To investigate the usefulness of prostaglandin E-major urinary metabolites (PGE-MUM) to distinguish CEAS from CD.

Research methods

Participants were diagnosed CEAS and CD by clinical diagnostic criteria and genetic analysis. All participants' PGE-MUM concentrations were measured by radioimmunoassay. We analyzed differentiating ability of PGE-MUM measurement between CEAS and CD.

Research results

Twenty patients with CEAS and 98 patients with CD were enrolled. It was found that the PGE-MUM concentrations of patients with CEAS were significantly higher than those of patients with CD and this correlation was still statistically significant after adjusting the possible confounding factors. Additionally, the present study showed the provisional cut-off value (48.9 $\mu\text{g/g} \times \text{Cre}$) of PGE-MUM had a differentiating ability with 95.0% sensitivity and 79.6% specificity (area under the curve 0.90).

Research conclusions

The measurement of PGE-MUM can serve as a useful biomarker to differentiate CEAS from CD, although genetic analysis is mandatory for the diagnosis of CEAS.

Research perspectives

Our study showed the usefulness of PGE-MUM to differentiate CEAS from CD. In the present research, the sample size of the patients with CEAS were relatively small, the cut-off value for

the distinction of CEAS from CD should be validated with large sample size of patients with CEAS in the future research.

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