Clinical Search for Undiagnosed Mesenteric Phlebosclerosis at Outpatient Departments Specializing in Herbal (Kampo) Medicine

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Abstract

Objective  Mesenteric phlebosclerosis (MP) is a disease characterized by calcification of the mesenteric vein, which causes chronic mesenteric ischemia. Recently, the long-term intake of gardenia fruit (‘Sanshishi’ in Japanese) has been attracting attention as a possible cause. Usually, only advanced, severe MP cases get reported. However, we suspected that some latent cases of this disease may exist.

We performed this study in order to determine the prediagnostic cases at our outpatient departments of herbal (Kampo) medicine, with particular attention paid to the initial changes, such as any slight color change of the colon, as shown in colonoscopy.

Methods  We recommend colonoscopy and computed tomography (CT) scans for patients with a long-term history of taking herbal medicines containing gardenia fruit. Clinical examinations were performed upon receiving patients’ consent from December 2013 to November 2014.

Results  Of the 103 patients who took gardenia fruit long-term, 29 agreed to be checked for MP. 14 patients underwent colonoscopy. Four patients were confirmed to have MP due to the presence of fibrotic deposition of the colonic membrane on histological inspection. Twenty-one patients underwent abdominal CT screening. Characteristic calcification of the mesenteric vein was observed on CT scans in 2 patients. All 4 MP patients took Kampo formulas containing gardenia fruit for more than 6.8 years. The other patients did not develop MP, despite long-term gardenia fruit intake.

Conclusion  We detected the latent and undiagnosed MP cases. All diagnoses were made while paying careful attention to any slight changes in colonoscopy and CT scans.

Key words: mesenteric phlebosclerosis, herbal medicine, Kampo medicine, gardenia fruit, sanshishi

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Introduction

Mesenteric phlebosclerosis (MP) is a comparatively new disease entity (1). Thus, its etiology has not yet been elucidated. Portal hypertension with liver dysfunction, diabetes mellitus, vasculitis, dialysis, hyperlipidemia and autoimmune disease have all been suggested as possible causes of MP (2-4). Despite this, the disease's exact cause remains unclear, so it is called IMP (idiopathic mesenteric phle-
undertaken without any overt symptoms. We also searched for undiagnosed cases of MP and investigated patients who received treatment from Kampo professionals at the outpatient department, and we searched for MP patients in his study took the common ingredient of gardenia fruit over a long period of time (8).

Diagnosing advanced cases of MP is relatively easy (1, 9). Calcification of the right hemicolon and the circumferential tissue characterize MP in its advanced stages. The bronze coloration of the colonic membrane is a hallmark for the diagnosis of MP (3, 9).

However, it is very difficult to detect this disease in the early stages. We often cannot identify calcification early in the course of the illness by X-ray examination (10). Thus, it is necessary to be aware of the presence of a thickened colon and an elevated computed tomography (CT) value in surrounding adipose tissue (2). In some cases, typical colonic color change cannot be seen under endoscopy. We can detect MP with a histological inspection in cases with mild blue coloration of the colonic membrane. Lack of attention to these initial changes can lead doctors to sometimes miss or misdiagnose MP.

Undiagnosed cases of MP may present without any clinical checkup, as it can be asymptomatic (8, 11). As such, the condition is considered to be a rare disease.

Until now, reported MP cases associated with Kampo medication were often at advanced stages. But we worried that there were still latent asymptomatic cases.

This study focuses on patients who used Kampo preparations containing gardenia fruit as one of the ingredients. We investigated patients who received treatment from Kampo professionals at the outpatient department, and we searched for the prediagnostic cases. We paid particular attention to the initial changes, such as a thickened colon and elevated CT values on CT scans, as well as slight color changes on colonoscopy. We also searched for undiagnosed cases of MP with more aggressive examinations than would normally be undertaken without any overt symptoms.

**Materials and Methods**

This study was conducted at the outpatient departments of Suwa Central Hospital and River Side Clinic in Nagano, Japan. We checked the clinical records and searched for patients with a history of taking Kampo preparations containing gardenia fruit from December 1, 2013 to November 30, 2014. We explained to the participants the potential risk of MP for patients with long-term (over two years) intake, and requested their consent to perform colonoscopy and abdominal plain CT.

Gardenia fruit is an ingredient in several kinds of herbal medicine. Two dosage forms of Kampo preparation are used: Extract preparations and traditional decocted herbal medicines. Kampo extract preparations that contain gardenia fruit are as follows: Bofutsushosan, Gorinsan, Inchinkoto, Kamikihito, Kamisyoyosan, Keigairengyoto, Orenchedokuto, Ryutansyakanto, Saikoseikanto, Seihaito, Seijobofuto, Shin’iseihaito, Shishihakuhito and Unseiin. We also used traditional medicines decocted with a mixture of crude drugs and water. There are many more types of traditional medicines than extract preparations.

We explained the significance of these examinations and consulted all patients with a history of the long-term use of Kampo preparations containing gardenia fruit. Although these proposed examinations could screen for other diseases, such as colorectal tumor, many patients declined the invitation due to unwillingness and fear.

The following diagnostic criteria in our hospital were used in this clinical study. The diagnosis of MP was confirmed with one of the following findings:

[A] Fibrotic deposition in the pericapillary region of the lamina propria on histological inspection (1) in a biopsy specimen collected from colonic membrane with mild blue coloration change or characteristic bronze change.

[B] Thickening of the affected colonic wall with calcification and associated calcification of the mesenteric vein and its tributaries on CT scans (9, 12).

We collect each one specimen each from the cecum, the ascending colon, the hepatic flexure, and the transverse colon where there was mild blue coloration change or characteristic bronze coloration change.

We collaborated with Dr. Asano, the pathologist in our hospital, for the histological evaluation of colonic biopsy specimen to determine the degree of fibrillization. These characteristics were developed to assist in diagnosing unidentified MP cases. They are as follows (Table 1):

<table>
<thead>
<tr>
<th>Fibrillization / Reduction of ductal cell density</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Significant fibrillization is not identified in the lamina propria.</td>
</tr>
<tr>
<td>Mild</td>
<td>Mild pericapillary concentric fibrillization is identified, but not associated with reduction of ductal cell density in the lamina propria.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate pericapillary concentric fibrillization is identified, associated with reduction of ductal cell density in part of the specimens.</td>
</tr>
<tr>
<td>Severe</td>
<td>Severe pericapillary concentric fibrillization is identified, associated with reduction of ductal cell density in almost all of the specimens.</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of Examined 29 Patients in This Study.

<table>
<thead>
<tr>
<th></th>
<th>Total patients n=29</th>
<th>MP patients n=4</th>
<th>non-MP patients n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>8 (27.6)</td>
<td>2 (50.0)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>21 (72.4)</td>
<td>2 (50.0)</td>
<td>19 (76.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>59.1 ± 3.0</td>
<td>63.8 ± 5.5</td>
<td>58.3 ± 3.3</td>
</tr>
<tr>
<td>Range (years)</td>
<td>16 - 86</td>
<td>49-75</td>
<td>16-86</td>
</tr>
<tr>
<td>Pre-existing disease or cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6 (20.7)</td>
<td>1 (25.0)</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>14 (48.3)</td>
<td>3 (75.0)</td>
<td>11 (44.0)</td>
</tr>
<tr>
<td>elevated LDL-c (%)</td>
<td>17 (58.6)</td>
<td>3 (75.0)</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>elevated TG (%)</td>
<td>9 (31.0)</td>
<td>2 (50.0)</td>
<td>7 (28.0)</td>
</tr>
<tr>
<td>Hepatic disease (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td>5 (17.2)</td>
<td>1 (25.0)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both colonoscopy and CT scan</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Colonoscopy only</td>
<td>8</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>CT scan only</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Duration of herbal medicine treatment (mean ± SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory visit (years)</td>
<td>9.6 ± 0.9</td>
<td>14.9 ± 0.7</td>
<td>8.7 ± 0.9</td>
</tr>
<tr>
<td>GF administration period (years)</td>
<td>6.5 ± 0.7</td>
<td>10.7 ± 1.3</td>
<td>5.9 ± 0.7</td>
</tr>
<tr>
<td>GF administration period (days)</td>
<td>2,378 ± 253</td>
<td>3,704 ± 431</td>
<td>2,167 ± 264</td>
</tr>
<tr>
<td>days of prescription drug</td>
<td>1,295 ± 178</td>
<td>2,909 ± 316</td>
<td>1,038 ± 145</td>
</tr>
<tr>
<td>Ratio of days of prescription drug / GF administration period</td>
<td>58.5 ± 5.6</td>
<td>80.2 ± 8.3</td>
<td>55.0 ± 6.1</td>
</tr>
</tbody>
</table>

CT: computed tomography, LDL-c: low-density lipoprotein cholesterol, TG: triglyceride, GF: Gardenia Fruit

*Comparison between MP patients and non-MP patients by Wilcoxon test.

Table 3. Chief Complaints to Administer Herbal Medicines Containing Gardenia Fruit.

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>31.0</td>
<td>cutaneous pruritus or dermatitis</td>
</tr>
<tr>
<td>4</td>
<td>13.8</td>
<td>obesity</td>
</tr>
<tr>
<td>4</td>
<td>13.8</td>
<td>rhinitis</td>
</tr>
<tr>
<td>3</td>
<td>10.3</td>
<td>neck stiffness</td>
</tr>
<tr>
<td>3</td>
<td>10.3</td>
<td>insomnia</td>
</tr>
<tr>
<td>2</td>
<td>6.9</td>
<td>feeling of cold and / or flushed face</td>
</tr>
<tr>
<td>1</td>
<td>3.4</td>
<td>irritation</td>
</tr>
<tr>
<td>1</td>
<td>3.4</td>
<td>frequent urination</td>
</tr>
<tr>
<td>1</td>
<td>3.4</td>
<td>dysosmia, smell disorder</td>
</tr>
<tr>
<td>1</td>
<td>3.4</td>
<td>anxiety</td>
</tr>
</tbody>
</table>

None: Significant fibrillization is not identified in the lamina propria.
Mild: Mild pericapillary concentric fibrillation is identified, but not associated with a reduction of ductal cell density in the lamina propria.
Moderate: Moderate pericapillary concentric fibrillation is identified and associated with a reduction of ductal cell density in part of the specimens.
Severe: Severe pericapillary concentric fibrillation is identified and associated with a reduction of ductal cell density in almost all of the specimens.

The Ethics Committee in Suwa Central Hospital approved this study. We were very careful not to reveal any personal information regarding the patients.

Results

Two hundred and forty patients took herbal medicines containing gardenia fruit. 103 patients had a history of long-term (2 or more years) gardenia fruit usage. Of these, 29 patients consented for colonoscopy and/or CT scan (Table 2). Cutaneous pruritus or dermatitis was the most frequent and main chief complaint in patients who used Kampo preparations containing gardenia fruit, followed by obesity and rhinitis (Table 3).

Of these 29 patients, six performed both colonoscopy and CT scan (Table 2). Eight patients underwent colonoscopy only, and 15 patients underwent CT scan only. Conse-
We investigated the duration of the patients’ ambulatory visits. We researched the administration period, or the duration from the beginning to the end of taking Kampo preparations containing gardenia fruit. The administration period (in years) of many patients did not correspond to the duration of ambulatory visit (in years) in patients accepted for colonoscopy (Fig. 1). All four diagnosed cases of MP were in patients who used gardenia fruit for more than 6.8 years. Those patients visited our department over a period of over 13.1 years (Fig. 1). Two patients without MP exceeded MP patients in terms of ambulatory visit duration.

Furthermore, we investigated the cumulative days of prescription drug, gardenia fruit administration period (days) and ratio of days of prescription drug/gardenia fruit administration period next (Table 2). In all 29 subjects, the cumulative days of the prescribed drug of many patients did not correspond to the gardenia fruit administration period (days) (Fig. 2). Many non-MP patients used the drug containing gardenia fruit intermittently (The spot below the straight line shows intermittent usage.) (Fig. 2).

Table 4 summarizes the background and findings of four MP cases. Below are the patient narratives for the four MP patients who were diagnosed following colonoscopy and CT scan, as well as a non-MP patient who took Kampo preparations containing gardenia fruit for a long time:

**MP case 1**

A 75-year-old man came to the hospital with complaints...
Figure 1. Relationship between GF administration period (years) and duration of ambulatory visit (years) in patients accepted for colonoscopy (n=14). GF: Gardenia fruit, MP: Mesenteric phlebosclerosis. Slanting dotted line shows the equivalent period.

Figure 2. Relationship between the number of cumulative days on which prescription drugs were used and the length of the GF administration period (in days) in patients examined in this study (n=29). GF: Gardenia fruit, MP: Mesenteric phlebosclerosis. Slanting dotted line shows the equivalent period.

of cutaneous pruritus for a duration of 16.3 years. He had a history of long-term use of decocted traditional medicine Unseiin, which contains gardenia fruit. He complained of occasional constipation and lower abdominal pain.

Abdominal CT scans showed wall thickening and linear calcification along the wall from the cecum to the transverse colon (Fig. 3a, b). Colonoscopy revealed dark blue mucosa extending from the cecum to the transverse colon. Redness and erosion of mucosa had been disseminated throughout the cecum and the ascending colon (Fig. 3c). Wall thickening and narrowing of lumen of the colon were also observed. Severe concentric fibrotic lesion in the pericapillary region of the lamina propria was observed on histological inspection (Fig. 3d-f). Because we identified the fibrillization associated with reduction of ductal cell density in almost all specimens, we considered the degree of fibrillization to be severe (Fig. 5c, f). All of these characteristic findings were typical for a confirmed diagnosis of MP. Examination of past medical history indicated that the patient had no calcification when an abdominal CT scan was performed three years ago. Therefore, we concluded that the calcification had formed within the past three years.

This patient was receiving Kampo medication at the time of this report; however, gardenia fruit was excluded from his prescription medications.
**MP case 2**

A 49-year-old woman suffered from chronic itching of her palms and feet (palmoplantar pustulosis). Her symptoms were ameliorated by a combined administration of Unseiin, Kamisyoyosan, Keigairengyoto and Orengedokuto for 12.2 years. CT scans did not reveal characteristic calcification, but an increased CT value, mild dilatation and slight calcification were present in the ileocecal vein (Fig. 4a). Colonoscopy was performed to identify possible MP, which showed mild blue coloration of the cecum and the ascending colon (Fig. 4b, c). Transparency of blood vessels was decreased. The histological findings of mild fibrotic lesions in pericapillary region of the lamina propria were also noted (Fig. 4d-f). The fibrillization was not associated with a reduction of ductal cell density in the lamina propria. Histological evaluation of the degree of fibrillization was mild (Fig. 5b, e). The patient was diagnosed with MP based on these findings.

Kampo treatment and follow up of MP continued at the time of this report. Kampo formulas containing gardenia fruit were omitted from treatment following the diagnosis.

**MP case 3**

A 64-year-old woman took herbal medicine to treat her various symptoms including flushed face, feeling of cold and menopausal symptoms. She had taken Kamisyoyosan for 11.4 years. Abdominal CT showed characteristic calcification of the cecum and the ascending colon. Colonoscopy was performed and mild blue coloration of the membrane on the cecum and the transverse colon were observed. Slight fibrotic depositions in the pericapillary region of the lamina propria were noted in the specimens collected at the hepatic flexure. Moderate and severe fibrotic lesions were also observed in the membrane of the cecum and the ascending colon. These findings led to a diagnosis of MP in this patient.

**MP case 4**

A 68-year-old man was treated with the decocted traditional medicine Unseiin. The treatment for cutaneous pruritus lasted 12.2 years. Colonoscopy showed typical bronze coloration of the mucosa extending from the cecum to the transverse colon. Histological inspection revealed severe concentric fibrotic lesions in pericapillary region of the lamina propria. Fibrillization associated with reduction of ductal cell density was identified in almost all specimens. The findings were characteristic of MP, and thus, sufficiently confirmed his diagnosis. This patient consented only to endoscopic screening, and

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**Figure 3. Clinical findings in MP Case 1.** a, b: Wall thickening and linear calcification along the right hemicolon (Computed tomography). c: Redness and erosion of mucosa in the cecum. (Colonoscopy) d: Severe fibrotic deposition in pericapillary region of the lamina propria. [Azan stain: (d) ×4, (f) ×20] [Hematoxylin and Eosin (H&E) staining: (e) ×20].

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gardenia fruit was excluded from his prescriptions.

**Non-MP case**

A 53-year-old woman requested Kampo treatments for rhinitis. She received Kampo medication for 6.9 years and used preparations containing gardenia fruit such as Orenge-dokuto, Kamisyoyosan, Bofutsusyosan and Shin’iseihaito for 6.6 years. Abdominal CT scans revealed no calcification along the colonic wall and the mesenterium. Moreover, we did not see any unusual color in her colonic membrane. Finally, no histological change was identified in biopsy specimens. In addition, no detectable fibrillization was found on histological evaluations (Fig. 5a, d).

Gardenia fruit was thereafter carefully prescribed to this patient.

**Discussion**

The mechanism of MP remains unclear (1). Although herbal drug use is unconfirmed in many MP cases, cases with long-term intake of herbal medicine have increased (5-8).

In this study, we actively sought latent cases of MP in a hospital that routinely and regularly prescribed herbal medicines. Although MP is considered to be a rare disease, we confirmed a relatively high rate of incidence this time. This discrepancy can be explained as noted below:

First of all, many doctors do not know this disease, so they do not readily recognize or diagnose it. Moreover, because this disease is often asymptomatic and develops latently, diagnosis is often delayed until the disease progresses without further examination (8, 11). Therefore, both medical staff and patients often miss it. We paid particular attention to this disease and consulted patients without MP symptoms, so we detected this disease at a high rate.

Next, we sought MP cases at professional outpatient departments of herbal (Kampo) medicine, in which herbal medicines are frequently used. It takes considerable time for this disease to develop. Until now, the average length of herbal treatment leading to development of MP was reported as 13.6 years in the largest-scale study (13). We identified this disease relatively early, but the average length of gardenia fruit administration period was 10.7 years (Table 2) in this study. Usually, few patients receive such long-term treatment. However, many patients received long-term treatment with herbal medicine in our outpatient departments. This factor led to a high positive rate.

Finally, identifying this disease early is difficult. In advanced MP cases, abdominal X-rays and abdominal plain CT scans demonstrate spotted or linear calcification around
the right hemicolon (3, 9). We often cannot detect calcification at during the early stage by X-ray examination (10). In this study, MP Case 2 demonstrated there was no characteristic calcification in MP Case 2, but mild dilatation and slight calcification in the ileocecal vein was observed (Fig. 4a). It is necessary to note both the presence of any slight calcification on CT scans. Moreover, we must be careful with colonic slight color change on colonoscopy. The change of color is pointed out by colonoscopy is mainly in the right side of the colon (9, 14, 15). The bronze mucosal coloration of mucosa is specific in advanced cases. In this examination, a severe case showed dark blue mucosa with mucosal erosion, wall thickening of the colon, and narrowing of the lumen were observed in a severe case (MP Case 1).

In addition, the coloration observed in a mild MP case (MP Case 2) was light blue. This slight color change was different from that observed in the cases showing progression.

No characteristic bronze coloration was noted, but the transparency of blood vessels of colonic membrane blood vessels was found to decrease in the early stage.

As described above, we may miss cases of MP during examinations unless we pay close attention to identifying the early symptoms associated with this disease.

Mesenteric circulatory failure may induce severe constipation, ileus, bowel dysfunction and ischemic colitis in advanced MP. Moreover, such severe cases have often been treated with either total or partial colectomy. Paying careful attention to the MP symptoms is therefore vital.

In the present study, a number of patients who received long-term treatment did not develop MP (Fig. 2). We thought that patients who used medicines containing gardenia fruit intermittently did not experience an onset of MP despite their long period of usage. We found a significant statistical difference regarding the cumulative prescription days and gardenia fruit administration period between MP and non-MP patients in our sample. The non-MP patients used a small amount of the drug containing gardenia fruit (p=0.0033). On the other hand, the MP patients used the same drug for a longer period of time (p=0.0341). Our results reflect the possibility that MP can be suppressed with Kampo medicine containing gardenia fruit intermittently and in small quantities.

Recently, gardenia fruit has drawn researchers’ attention because it can potentially cause MP. The essential pathology of MP is circulatory failure of the colon due to calcification of the mesenteric vein (1). The majority of drugs, including herbal medicines, are absorbed in the right-sided colon. Gardenia fruit gets absorbed in the same region. Therefore, we suggest a direct effect against colonic mucosa and the mesenteric vein during drug absorption is postulated (5).

The gardenia fruit is one of the most useful herbal medicines among Kampo treatments. Herbal medicines containing gardenia fruit, such as Kamisyoyosan, are used for menstrual irregularity, hot flashes, and perimenopausal symptoms (16, 17). They are also used for dermatological disorders like cutaneous pruritus (18, 19). Unseiin, a traditional medicine, is prescribed for pruritic cutaneous diseases as well as menoxyenia and hot flashes, symptoms often associ-

**Figure 5.** Histological criterion for the degree of fibrillization in our hospital. [None]: Significant fibrillization is not identified in the lamina propria (a, d: Non-MP Case). [Mild]: Mild pericapillary concentric fibrillization is identified, but not associated with a reduction of ductal cell density in the lamina propria (b, e: MP Case 2). [Moderate]: Moderate pericapillary concentric fibrillization is identified and associated with a reduction of ductal cell density in part of specimen. [Severe]: Severe pericapillary concentric fibrillization is identified and associated with a reduction of ductal cell density in almost all of specimen (c, f: MP Case 1). a, b, c: [Azan stain: ×10]. d, e, f: [H&E staining: ×10].

ated with menopausal disorders. People use herbal medicines containing gardenia fruit for otoaryngology diseases, such as allergic rhinitis and sinusitis. They also successfully treat insomnia, depression, and vertigo (20). The Kampo medicines Orengedokuto and Bofutsushosan regulate hypertensive and gieriatric diseases. They are also sometimes used for obese patients. They are often necessary to improvement a patient’s quality of life (21, 22). Bofutsushosan for obesity and Kamisyoyosan for gynecologic disease are quite frequently used.

Kampo extract is an achievement of modern medicine. Its use for many diseases has increased in recent years. But long-term gardenia fruit consumption is attracting attention as a possible cause of MP. Herbal medicines containing gardenia fruit must be prescribed carefully. However, avoiding gardenia fruit use entirely may be difficult for some patients. The results of this study indicate that intermittent use is favorable.

Extensive investigation is thus needed to clarify MP’s etiology and pathology. For many MP cases, herbal drug use remains unconfirmed. A definitive correlation between a pre-existing disease and the onset of MP remains unclear. Additional investigation with a larger patient population and further verification of other risk factors is therefore needed.

The authors state that they have no Conflict of Interest (COI).

References