Clinical characteristics of asymptomatic Terson syndrome in the patients with aneurysmal subarachnoid hemorrhage

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Received: 2019-05-01        Accepted: 2019-09-24

Abstract
● AIM: To investigate clinical characteristics of asymptomatic Terson syndrome and its clinical impact in patients with aneurysmal subarachnoid hemorrhage (SAH).
● METHODS: This retrospective, interventional study included 31 patients with aneurysmal SAH, and the medical records were reviewed. In addition to baseline characteristics of the study population such as age, sex, and underlying medical history, multi-modal imaging analysis, including fluorescein angiography (FA), spectral domain optical coherence tomography (SD-OCT), were also reviewed. Glasgow Coma Scale (GCS), Hunt-Hess (HH) grade, and Fisher scale at the time of admission, and functional outcome by using modified Rankin Scale (mRS) at 6mo were compared.
● RESULTS: Of the 31 patients, 10 patients (32.3%) were diagnosed with Terson syndrome. All the patients with Terson syndrome did not report visual symptoms at the time of ophthalmologic screening. FA showed microvascular changes of retinal capillaries and varying degrees of disc leakage. SD-OCT allowed intuitive anatomical localization of multi-layered retinal hemorrhages and assessment of ellipsoid zone integrity. The patients with Terson syndrome showed significantly worse GCS (P=0.047) and HH grade (P=0.025) than those without, except Fisher scale (P=0.385). There was no significant difference in the mRS (P=0.250) at 6mo. Among baseline factors, the HH grade was the only significant factor associated with Terson syndrome (B=1.079, P=0.016).
● CONCLUSION: In our study, 32.3% of the patients have Terson syndrome without visual symptoms. The baseline HH grade is significantly correlated with Terson syndrome, and there is no significant difference in the functional outcome between the patients with and without Terson syndrome. Terson syndrome may develop without any visual symptoms as shown in our study, and ophthalmologic screening may be recommended to prevent further visual deterioration especially in the patients with poor HH grade at the time of aneurysmal SAH.
● KEYWORDS: cerebral aneurysm; subarachnoid hemorrhage; Terson syndrome

INTRODUCTION

Terson syndrome, which was first described in 1900 by Albert Terson1, and it was previously defined as vitreous hemorrhage associated with subarachnoid hemorrhage (SAH). However, additional features have been reported including various retinal hemorrhages, such as intraretinal, subretinal, and sub-internal limiting membrane (ILM) hemorrhage2-4. The macular “double ring” sign, associated with both sub-ILM hemorrhage and subhyaloid hemorrhage, has also been reported in this disease5. These additional findings have widened the definition of Terson syndrome. As a result, Terson syndrome currently is defined as hemorrhages into any of the retinal spaces, secondary to an acute rise in intracranial pressure (ICP).

Although it has been over 100y since its first description, the exact pathophysiology of Terson syndrome remains a subject of investigation. The optic nerve is covered by the optic nerve sheath, which is derived from three layers of meninges, and the cerebrospinal fluid moves freely between the intracranial and intraorbital subarachnoid spaces7. Thus, both intracranial and
intraorbital subarachnoid spaces can be affected by the same pressure change[^8]. One hypothesis is based on these features and proposes that a sudden onset of intracranial hypertension forces blood or cerebrospinal fluid under high pressure into the intraorbital subarachnoid space. This increased pressure then causes compression of the central retinal vein (CRV) in the subarachnoid space and the intervascular space of the optic nerve, leading to venous hypertension and rupture of the retinal veins and capillaries[^9-11]. An alternative hypothesis is that increased ICP is transmitted throughout the venous channels into the orbital veins, rather than through the subarachnoid sheath spaces[^12-13].

Because ophthalmologic screening for Terson syndrome is not considered as a routine examination, Terson syndrome is concomitantly diagnosed with computed tomography or ultrasonography during brain evaluation[^14-16]. Thus, with the widened definition, Terson syndrome remains an under-estimated surgical intervention for aneurysmal SAH. In addition, recent studies involving the use of advanced surgical techniques have shown rapid visual recovery in patients with Terson syndrome, supporting the necessity of early detection and surgical intervention for this condition[^21-23].

Notably, although our understanding of Terson syndrome has improved, few studies have investigated multi-modal imaging analysis for Terson syndrome. In this study, we investigated clinical characteristics of Terson syndrome including multi-modal imaging analysis in the patients with aneurysmal SAH. In addition, we investigated if there is any difference in baseline and final functional outcome between the patients with and without Terson syndrome.

**SUBJECTS AND METHODS**

**Ethical Approval** This retrospective, observational study was performed at the Catholic Kwandong University, International St. Mary’s Hospital. The study protocol was approved by the Institutional Review Board of International St. Mary’s Hospital, Catholic Kwandong University College of Medicine, and it adhered to all tenets of the Declaration of Helsinki. Due to the retrospective nature of this investigation, the need for informed consent from each patient was waived, and this waiver was also approved by the Institutional Review Board.

**Subjects** In our hospital, routine ophthalmologic screening is usually performed in the patients with aneurysmal SAH. Thus, we could retrospectively reviewed the medical records of patients who underwent ophthalmologic evaluation after surgical intervention for aneurysmal SAH at Department of Neurosurgery, International St. Mary’s Hospital, from September 2016 to August 2018, and completed at least 6-month of follow-up.

**Ophthalmologic Screening for Terson Syndrome in Patients with Aneurysmal Subarachnoid Hemorrhage**

Ophthalmologic examinations, including a slit lamp examination, an intraocular pressure measurement using a non-contact tonometer, and a fundus examination were performed. Refractive error for each eye was measured using an autorefractor and then converted to spherical equivalents [diopters (D)]. Best-corrected visual acuity (BCVA) was measured by decimal visual acuity chart and then converted to the logarithm of the minimum angle of resolution (logMAR) scale. Multi-modal imaging studies included fluorescein angiography (FA), fundus auto fluorescence (FAF), and spectral domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering) with an EDI modality. Optos Daytona ultrawide-field retinal imaging system (P200T; Optos plc, Dunfermline, UK) was used for ultrawide fundus photography. FA was performed using the Heidelberg Retina Angiograph system (HRA-2; Heidelberg Engineering, Dossenheim, Germany), with a confocal scanning laser ophthalmoscope.

**Baseline Characteristics and Functional Outcome of Patients with Aneurysmal Subarachnoid Hemorrhage**

We retrospectively reviewed the medical records of patients who underwent ophthalmologic evaluation after surgical intervention for aneurysmal SAH, and the data collected included sex, age, medical history, presence of hydrocephalus, and location of cerebral aneurysm. The admitting Glasgow Coma Scale (GCS), Hunt-Hess (HH) grade, and Fisher scale were evaluated for each patient. The GCS were further classified into three categories: mild (score 13 to 15), moderate (score 9 to 12), and severe (score 3 to 8). Functional outcome was evaluated by using modified Rankin Scale (mRS) at 6mo after aneurysmal SAH.

**Statistical Analysis** Data are presented as the mean±standard deviation (range), unless otherwise indicated. IBM SPSS Statistics software for Windows, version 22.0 (IBM Corporation, Somers, NY, USA) was used for statistical analyses. For subgroup comparison, Mann-Whitney U test was used for continuous variables, and Chi-square test was used for categorical variables. We also evaluated the possible factors associated with Terson syndrome by using binary logistic regression analysis. Baseline factors included age at the time of aneurysmal SAH, sex, GCS, HH, and Fisher grade. Mauchly’s test of sphericity and Kolmogorov-Smirnov analyses were used to confirm statistical validity. *P*<0.05 was defined as statistically significant.
RESULTS
Baseline Characteristics of the Study Population A total of 31 patients with aneurysmal SAH were retrospectively included in this study; 9 patients (29.0%) were male, and the mean age was 53.5±10.3y (range 32-73y). The mean follow-up duration was 9.5±5.8mo (range 6-20mo).

Clinical Findings in Terson Syndrome Of these 31 patients, 16 patients (31.6%) showed fundus abnormalities during ophthalmologic evaluation, and 10 (32.3%) were diagnosed with Terson syndrome. Other 6 patients showed retinal changes such as simple retinal hemorrhage, Roth-spot like hemorrhage, and cotton spots, however these patients were not diagnosed as Terson syndrome because retinal findings were not consistent with the definition of Terson syndrome. Clinical characteristics of patients with Terson syndrome are shown in Table 1.

Multi-layered retinal hemorrhages resolved spontaneously over an average of 3.8±2.0mo (range 1-7mo). The mean BCVA was 0.2±0.2 logMAR (range 0-0.7 logMAR) at the time of diagnosis, and 0.1±0.1 logMAR (range 0-0.3 logMAR) at the last follow-up. None of the patients underwent intraocular surgery for Terson syndrome.

Retinal Findings by Ultra-wide Fundus Photography Fundus examination showed multi-layered retinal hemorrhages, including subretinal, intraretinal, sub-ILM, preretinal, and vitreous hemorrhages in the patients with Terson syndrome (Figure 1).

Fluorescein Angiography Findings of Terson Syndrome FA analysis showed blocked fluorescence, corresponding to multi-layered retinal hemorrhages in patients with Terson syndrome. Mild increased tortuosity of retinal capillaries, particularly those in the perifoveal area, and a few microaneurysms (MAs) were found in the patients. However, FA of each patient did not show definite retinal vascular obstruction or vascular leakage. We also noted variable degrees of disc leakage among the patients with Terson syndrome. Profuse disc leakage was observed in some patients, regardless of presence of disc swelling on fundus examination. The representative FA images of patients with Terson syndrome are shown in Figure 2.

Spectral Domain Optical Coherence Tomography Findings of Terson Syndrome SD-OCT enhanced intuitive visualization for multi-layered retinal hemorrhages in these patients. These hemorrhages were located throughout the retina, from the subretinal to the preretinal space. In addition, photoreceptor ellipsoid zone integrity could be evaluated by SD-OCT. The representative SD-OCT images in patients with Terson syndrome are shown in Figure 3.
Fundus Autofluorescence Images of Terson Syndrome

On FAF images, multi-layered retinal hemorrhages appeared as blocked hypo-autofluorescent lesions at the time of diagnosis. This hypo-autofluorescence differed, depending on the location of multi-layered retinal hemorrhages. This hypo-autofluorescence was spontaneously resolved during follow-up, although hypo-autofluorescence corresponding to subretinal hemorrhage was still apparent, even after resolution of multi-layered retinal hemorrhage (Figure 4).

**Figure 2 FA findings of patients with Terson syndrome**  
A-D: FA findings of a 59-year-old female patient with bilateral Terson syndrome. Microaneurysmal changes with blocked fluorescence due to retinal hemorrhages in the early phase (A, right eye; B, left eye). In the late phase, mild disc leakage in the right eye (C) and diffuse leakage in the left eye (D) were observed. E-H: FA findings of a 48-year-old female patient with unilateral Terson syndrome in the left eye. This patient showed bilateral disc swelling. Microaneurysmal changes and increased tortuosity of microvasculature at the perifovea in early phase (E, right eye; F, left eye). Blocked fluorescence due to retinal hemorrhages and vitreous hemorrhage was also noted in the left eye (F). In the late phase, diffuse disc leakage was noted in both eyes (G, right eye; H, left eye). I-L: FA findings of a 60-year-old female patient with unilateral Terson syndrome. FA showed microaneurysmal changes and increased tortuosity of the microvasculature at the perifovea in the early phase (I, right eye; J, left eye). Blocked fluorescence due to retinal hemorrhages was also noted in the left eye (J). In the late phase, disc staining in the right eye (K) and mild disc leakage in the left eye were noted (L).

**Fundus Autofluorescence Images of Terson Syndrome**

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### Comparison of Baseline Characteristics and Postoperative Functional Outcome Between the Patients with and Without Terson Syndrome

When compared with the patients without Terson syndrome, those with Terson syndrome showed significantly worse GCS ($P=0.047$) and HH grade ($P=0.025$) at the time of admission. There was no significant difference in Fisher scale ($P=0.385$). Six months after aneurysmal SAH, there was no significant difference in the mRS ($P=0.250$) between two groups. The comparison of patients’ characteristics is shown in Table 2. In addition, the location of cerebral aneurysm was not significantly different between the patients with and without Terson syndrome (Table 3).

### Predictive Factors Associated with Presence of Terson Syndrome in Patients with Aneurysmal Subarachnoid Hemorrhage

We performed binary logistic regression analysis to investigate the predictive factors associated with presence of Terson syndrome in aneurysmal SAH patients. Baseline factors included age, sex, and presence of hydrocephalus. The admitting GCS, HH grade, and Fisher grade were also included. The HH grade was the only significant factor associated with Terson syndrome ($B=1.079, P=0.016$).
**DISCUSSION**

In this study, we investigated characteristics of Terson syndrome including multi-modal imaging analysis and its clinical outcome in patients with aneurysmal SAH. Among our study population, 32.3% of the patients were diagnosed as Terson syndrome, and all denied any visual symptoms at the time of diagnosis. FA analysis showed microvascular changes, such as increased microvascular tortuosity in the macular area and MAs. However, there were no significant changes in retinal arteries and veins such as obstruction or increased tortuosity. In addition, despite clinical presentations of Terson syndrome.
syndrome were asymmetric, FA showed similar perifoveal microvascular tortuosity and MAs in both eyes, suggesting symmetric vascular changes. Varying degrees of disc leakage on FA were also found in patients with Terson syndrome. We speculate that the different degrees of disc leakage on FA may reflect varying degrees of rupture in the peripapillary capillaries in Terson syndrome. Previous case reports have suggested that the optic nerve head and peripapillary area are the major sites involved in the pathogenesis of Terson syndrome[24-25]. One case study showed dye leakage at the margin of the disc in a patient with Terson syndrome, whereas the contralateral eye did not show disc leakage with FA[24]. Because the leakage site corresponded to the demarcation between the ILM of the retina and the ILM of Elschnig, the authors speculated that intracranial hypertension on the terminal subarachnoid space of the optic nerve sheath may induce damage to the border tissue of Elschnig, the border tissue of Jacoby, the intermediary tissue of Kunt, the peripapillary retina, and the ILM[24]. Another case study reported high papillary endoglin expression, indicating activation of endothelial cells[25]. In this case, the authors suggested that peripapillary activation of the capillaries occurred after the onset of Terson syndrome[25]. They further speculated that increased ICP may be transmitted through the optic nerve sheath to optic nerve head, leading to occlusion of the retinal and choroidal anastomoses at the level of the lamina cribrosa[25]. Thus, together with previous findings, varying degrees of disc leakage in Terson patients may highlight the importance of the optic disc and the peripapillary area in the pathogenesis of Terson syndrome.

In addition, we speculate that there may be ‘thresh-hold’ for development of multi-layered hemorrhages in the patients with aneurysmal SAH. One possibility is that anatomic variations at the level of the lamina cribrosa or in the retrolaminar portion of the optic nerve may lead to asymmetry, even in the presence

Table 3 Location of cerebral aneurysm in the patients with and without Terson syndrome

<table>
<thead>
<tr>
<th>Aneurysm location</th>
<th>Patients with Terson syndrome (n=10)</th>
<th>Patients without Terson syndrome (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal carotid artery</td>
<td>2 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>5 (50.0)</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>0</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>2 (20.0)</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>1 (10.0)</td>
<td>5 (23.7)</td>
</tr>
<tr>
<td>Superior hypophyseal artery</td>
<td>0</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Anterior choroidal artery</td>
<td>0</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Paraclinoid artery</td>
<td>0</td>
<td>1 (4.8)</td>
</tr>
</tbody>
</table>

There was no statistically significant difference between two groups by Chi-square test (P=0.291).
Characteristics of asymptomatic Terson syndrome

of identical levels of increased ICP and subarachnoid space pressure. The CRV are naturally compressed as it penetrates through the rigid sieve-like openings in the lamina cribrosa. Thus, these vessels are relatively sensitive to compression from mechanical stretching of the lamina cribrosa. Consequently, anatomic variation in the right and left lamina cribrosa or retrolaminar space may lead to a differential susceptibility to pressure changes in the optic nerve sheath and/or subarachnoid space. These different degrees of vascular compression could result in the asymmetric presentation of Terson syndrome in some patients. Another hypothesis is that there are local differences in the pressure transmitted to the optic nerve sheath or intraorbital vein. Thus, if the transmitted pressure is different for each eye, this would result in different degrees of venous hypertension and a presentation of asymmetric Terson syndrome.

However, there is still an unsolved question for the pathogenesis of Terson syndrome. In our study, there were no significant change in retinal arteries and retinal vein, unlike hypertensive retinopathy or retinal vascular obstructive diseases. This may due to the fact that Terson syndrome is associated with abrupt, but transient change of ICP in patients with aneurysmal SAH. In addition, multi-layered retinal hemorrhages may develop in other conditions such as leukemia. There may be concomitant pathogenesis between Terson syndrome and other conditions which are not still uncovered. Or, simply, similar manifestation, but different pathogenesis may exist in these patients. Thus, further investigations for revealing the pathogenesis of multi-layered retinal hemorrhages are needed to prove this unmet need.

In our study, ultrawide fundus photography, SD-OCT, and FAF evaluations are helpful for patient screening and monitoring during follow-up period. Ultrawide fundus images provide an over view of retinal status, which is helpful at the time of diagnosis and follow-up. SD-OCT is helpful for intuitive localization of multi-layered retinal hemorrhages and the evaluation of photoreceptor ellipsoid zone integrity in patients with Terson syndrome. Using FAF, hypo-autofluorescent lesions that were associated with multi-layered retinal hemorrhages were visualized at the time of diagnosis, then spontaneously resolved concurrent with resolution of hemorrhages. Only hypo-autofluorescence that corresponded to subretinal hemorrhage was not completely resolved during follow-up, suggesting damage of the retinal pigment epithelium.

After ophthalmologic evaluation, we also investigated clinical outcome of Terson syndrome in aneurysmal SAH patients. The GCS and HH grade were significantly worse in the patients with Terson syndrome than those without, which was consistent with previous studies. However, the mRS was not significantly different between the patients with and without Terson syndrome, which were not consistent with the results of previous studies. In our study population, most of patients showed good functional outcome (mRS 0 in 18 patients and 1 in 7 patients). Those with severe disability was only 2 patients (mRS 4 and mRS 5 for only 1 patient, respectively), and no mortality associated with aneurysmal SAH. The presence of Terson syndrome may be one of manifestations reflecting worse baseline condition in the patients with aneurysmal SAH, but not directly associated with worse functional outcome in these patients. Or, simply, prompt surgical intervention and improved perioperative care for the patients with aneurysmal SAH may lead to improvement of clinical outcome in this study. However, we also found that 3 patients with mild GCS at the time of admission showed Terson syndrome, which was not consistent with previous studies.

One study previously suggested that Terson syndrome also developed in some patients without raised ICP or initial unconsciousness. Based on these results, Terson syndrome may be multi-factorial disease and other factors such as previously suggested personal susceptibility for ‘thresh-hold’ other than ICP may involve in the pathogenesis, resulting in this discrepancy. If so, functional outcome may not be different between the patients with and without Terson syndrome, as shown in our study. However, we also admit that there may be selection bias in our study population, because 4 patients were dead just before and after surgery and could not undergo ophthalmologic screening during the study period. Thus, further study is recommended including ophthalmologic screening at the time of diagnosis of SAH or right after surgery for SAH may be needed to minimize this selection bias.

In our study, all the patients with Terson syndrome denied any visual symptoms at the time of ophthalmologic screening, even in the presence of vitreous hemorrhage. Thus, we recommend ophthalmologic screening for Terson syndrome in the patients with aneurysmal SAH. Although visual outcome of Terson syndrome in our study population was relatively good, Terson syndrome may lead to permanent visual deterioration due to various complications such as epiretinal membrane, retinal detachment or proliferative vitreoretinopathy. Currently, advancement of surgical intervention seems to result in good surgical outcome for Terson syndrome. Thus, possibility of Terson syndrome should be kept in mind, and ophthalmologic screening for Terson syndrome is needed for patients with aneurysmal SAH, especially patients with worse HH grade at the time of admission. Our study has several limitations, including its retrospective design and relatively small study population. Previous studies have suggested that the degree of increased ICP may be associated with the development of Terson syndrome.
However, because ICP measurement is not included during routine examination in our hospital, this study lacks ICP values. Importantly, the inclusion of ICP measurements in future studies would allow investigation of the association between this metric and the various manifestations of Terson syndrome. In addition, here we included only aneurysmal SAH patients, as routine consultation for Terson syndrome is currently performed for these patients in the ophthalmology and neurosurgery departments in our hospital. In future prospective studies, use of a broadened screening population, incorporation of additional examinations, including measurement of ICP, and a planned long-term follow-up period may further enhance our understanding of the pathophysiology of Terson syndrome.

With some limitations, however, this study is the first attempt to investigate the prevalence of Terson syndrome in Asian population. In addition, we focused on the clinical characteristics of Terson syndrome by using multi-modal imaging analyses. In our study, Terson syndrome may be asymptomatic in some patients, even in the presence of vitreous hemorrhage or preretinal hemorrhage. We also found that half of the patients with Terson syndrome had bilateral asymmetric or unilateral Terson syndrome. These findings may be one of reasons for under-estimation of Terson syndrome. Further studies with much larger study population may improve our knowledge of Terson syndrome.

In conclusion, 32.3% of the study population had Terson syndrome without any visual symptoms in the patients with aneurysmal SAH in our study. Multi-modal imaging analysis of Terson syndrome showed various characteristic features of Terson syndrome, improving our understanding of this complex disease. The baseline HH grade was significantly correlated with the presence of Terson syndrome, and the presence of Terson syndrome was not significantly associated with functional outcome in our study. We recommend ophthalmologic screening for Terson syndrome seems to be helpful to prevent further visual deterioration, especially those with worse baseline condition at the time of admission.

ACKNOWLEDGEMENTS

Foundation: Supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No.2018R1C1B5085620).

Conflicts of Interest: Kang HM, None; Cho JM, None; Kim SY, None; Choi JH, None.

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