Prognostic Factors Affecting Visual Recovery in Terson Syndrome with Aneurysmal Subarachnoid Hemorrhage

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Background: The purpose of this study was to survey the anatomical angiographic finding of the aneurysm and identify parameters associated with visual recovery of the patients with Terson syndrome (TS).

Methods: This retrospective study was conducted on 494 patients with aneurysmal subarachnoid hemorrhage (SAH) from 2008 to 2015. Radiologists independently reviewed findings on computed tomography scans and cerebral digital subtraction angiography. Ophthalmologists conducted ophthalmological examinations for patients who had no communication problem. The degree of visual acuity recovery (DVAR) was measured based on the visual acuity difference between the initial and sixth-month follow-up. Favorable visual recovery was defined as DVAR >0.4.

Results: A total of 494 patients diagnosed with aneurysmal SAH were given admission to a single institute, of whom 171 received ophthalmological examinations. Of the total, 40 patients were diagnosed with TS and 54 eyeballs were affected by vitreous or retinal hemorrhage. In the multivariable analysis, male sex (odds ratio [OR] 9.530; 95% confidence interval [CI] 1.824-49.801), favorable Glasgow coma scale (GCS) (≥13 points) (OR 8.073; 95% CI 1.226-53.148), and anterior orientation of aneurysm (OR 5.006; 95% CI 1.842-29.751) were identified as independent factors predicting favorable visual recovery after adjusting covariables.

Conclusion: TS was identified in 23.4% of patients with aneurysmal SAH. Male sex, favorable GCS at admission, and anterior orientation of the aneurysm were identified as prognostic factors for favorable visual recovery. It is proposed that positive ophthalmologic consultation and treatment can be helpful in improving vision and quality of life of TS patients.

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Key words: Prognosis; Visual acuity; Subarachnoid hemorrhage

INTRODUCTION

In 1881, the German ophthalmologist, Moritz Litten, first described the incident of vitreous bleeding with subarachnoid hemorrhage (SAH).[1] Terson syndrome (TS) was first described by the French ophthalmologist, Albert Terson in 1900,[2] as vitreous or subhyaloid hemorrhage secondary to intracerebral hemorrhage and the main cause of the syndrome is SAH from a ruptured intracranial aneurysm.[3] The intraocular hemorrhages of any type (retinal, subhyaloid or vitreous) have been documented in 10-40% of individuals with SAH.[4]

The mechanism underlying TS remains as controversial and poorly understood. Currently, it has been proposed that a sudden increase in intracranial pressure passed via the optic nerve sheath to the optic nerve head obstructs the central vein and retinochoroidal anastomosis at the optic nerve head.[5] The subsequent rising intravascular pressure causes retinal venous stasis, resulting in intraocular hemorrhage.[6]

In this study, we investigated the incidence of intraretinal and vitreous hemorrhage, identified aneurysmal location or orientation based on 4-vessel digital subtraction angiography (DSA) or computed tomographic (CT) angiography and the prognostic parameters associated with visual recovery of patients suffering from SAH.

METHODS

Demographic data for all patients were obtained from a retrospectively maintained database. The study was conducted after approval from the institutional review board of Ajou University medical center (AJIRB-MED-MDB-17-037). Between September 2008 and April 2015, the patients were admitted to a single institute and diagnosed with a rupture of an intracranial aneurysm. The diagnosis of ruptured aneurysms was established by CT angiography scan and cerebral DSA to demonstrate an underlying aneurysm within 12 hours of the admission. Within seven days after surgical treatment for the aneurysm, the ophthalmologists performed ophthalmological examinations including visual acuity, pupillary reflexes, and fundoscopic appearance after induced mydriasis, except for ruptured arteriovenous malformation and non-aneurysmal SAH or the patients who could not read and speak at the time of vision test. The visual acuity was measured using Yong-Han Jin's distance visual acuity test. The visual acuity difference between the initial and sixth-month follow-up was expressed as the degree of visual acuity recovery (DVAR). Favorable visual recovery was defined as an improvement of three lines or more compared to the initial visual acuity with reference to the reports by Lee and Kim[7] and Jeong et al.[8] The DVAR

were divided into unfavorable and favorable recovery groups based on 0.4. TS was classified as retinal, vitreous or mixed retinal to vitreous hemorrhage for this study.

The initial clinical status of patients was evaluated based on Hunt and Hess (HH) grade, Fisher classification and Glasgow coma scale (GCS) score at the time of emergency department admission. The anatomical location and orientation (using CT angiography and cerebral DSA) of the studied aneurysms were recorded by radiologists. The neurosurgeon performed surgical clipping or endovascular coiling within 24 hours of admission.

The factors affecting visual recovery were investigated using the multivariate logistic regression analysis. SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Mann-Whitney test was used to compare visual recovery and variables between the groups, and Fisher's exact test was used to compare categorical variables. Statistical significance was defined when the P was less than 0.05.

RESULTS

Totally 494 patients with aneurysmal SAH were admitted in a single institute between September 2008 and April 2015 and ophthalmologists performed ophthalmologic examinations on 171 patients. The mean age of the patients was 44.3 years (range 27-67 years). Three-hundred-twenty-three patients were excluded from ophthalmologic examinations based on high severity and the patients did not want to be examined nor had any symptoms. Patients with insufficient medical records were excluded from enrollment. Of the 171 patients, 40 were diagnosed with TS, and 131 were non-TS. Of the total 40 patients, 24 were men and 16 were women. Analysis of our data revealed no statistically significant difference between men and women (χ^2=0.0439, df=1, P=0.563), and anterior orientation of an aneurysm (χ^2=0.0021, df =1, P=0.872) with regard to the incidence of TS. The difference in the incidence of TS among patients with admitting GCS score ≥13 points and those with GCS score <13 reached statistical significance (χ^2=28.198, df=1,

P=0.002). The incidence of TS was higher among the patients with HH grade (χ^2=47.052, df=1, P=0.001) and Fisher grade (χ^2=52.768, df=1, P=0.001) more than 2 points (Table 1).

In 40 patients with TS (23%), 54 eyeballs were affected by vitreous or retinal hemorrhage related to aneurysmal SAH including 38 (70.4%) with vitreous hemorrhage, 12 (22.2%) with retinal hemorrhage, and 4 (7.4%) with mixed vitreous and retinal hemorrhage. Bilateral ocular hemorrhage was identified in 14 (35%) patients, whereas right and left side eye was affected in 12 (30%) and 14 (35%) patients, respectively. In the first CT performed in the emergency department, intraocular hemorrhage was observed in 10 patients (25%) in right side eye, in 11 patients (27.5%) in left side eye and in 12 (30%) in bilateral eyes. However, no ocular hemorrhage was observed in 7 patients (17.5%).

Of the 40 patients, patients with underlying eye disease included one case with cataract, one case with corneal opacity and two cases with intravitreal implantation. Initial ophthalmological evaluation (mean 7 days; range 1-117 days) was performed in thirteen eyes (24.1%) within seven days. Mean duration of follow-up ophthalmological examination was six months (range 2-36 months). Ophthalmologic interventions were considered according to the ophthalmologist's decision in case of no improvement of bleeding on follow-up examination despite conservative treatment. Twenty-six (48.1%) of 54 eyes were treated by ophthalmologic interventions like trans pars planar vitrec-

Table 1. Characteristics of TS and non-TS in 171 patients with aneurysmal SAH

Variable	No. of TS (n=40)	No. of non-TS (n=131)
Sex		
Male	24 (60)	77 (58.8)
Female	16 (40)	54 (41.2)
Fisher grade		
≤2	3 (7.5)	115 (87.8)
>2	37 (92.5)	16 (12.2)
HH grade		
≤2	6 (15)	108 (82.4)
>2	34 (85)	23 (17.6)
GCS score		
<13	22 (55)	14 (10.7)
≥13	18 (45)	117 (89.3)
Location of aneurysm		
Anterior circulation*	33 (82.5)	84 (64.1)
Posterior circulation†	7 (17.5)	47 (35.9)
Orientation of an aneurysm		
Anterior	14 (35)	62 (47.3)
Others	26 (65)	69 (52.7)

TS, Terson syndrome; SAH, subarachnoid hemorrhage; HH, Hunt and Hess; GCS, Glasgow coma scale.
Values are presented as number (%).
*Anterior communicating artery, middle cerebral artery, posterior communicating artery, anterior choroidal artery, and internal carotid artery.
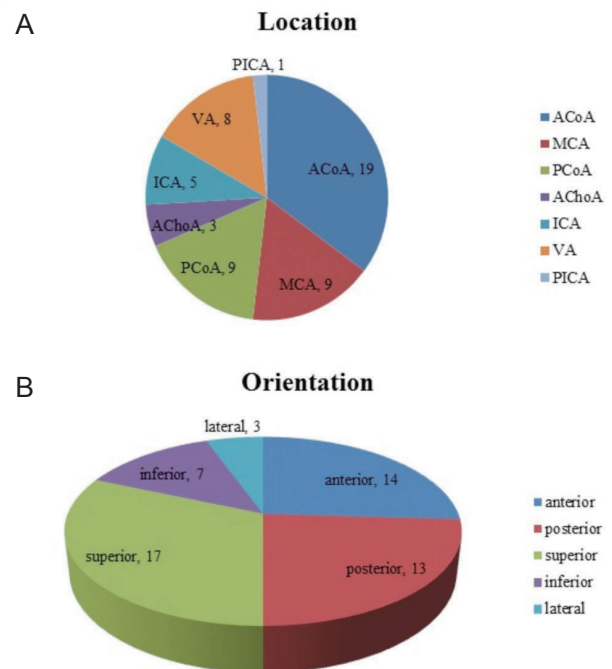†Vertebral artery and posterior inferior cerebellar artery.

Figure 1. Angiographic finding of an anatomical aneurysm in 54 eyes with Terson syndrome. Distribution of location of the aneurysm (A) and orientation of the aneurysm (B). ACoA, anterior communicating artery; MCA, middle cerebral artery; PCoA, posterior communicating artery; AChoA, anterior choroidal artery; ICA, internal carotid artery; VA, vertebral artery; PICA, posterior inferior cerebellar artery.

tomy (TPPV), intra-vitreous Avastin (Bevacizumab; Roche, Basel, Switzerland) injection or laser photocoagulation.

Data and statistical values of 54 eyes with respect to sex, age, HH grade, Fisher grade, GCS score, neurosurgical treatment type, and ophthalmologic intervention were presented,

Table 2. Characteristics and DVAR of 54 eyes with Terson syndrome

Variable	No. of eyes	Mean DVAR	P value
Sex			0.001*
Male	31 (57.4)	0.53	
Female	23 (42.6)	0.24	
Age			0.175
≤45	24 (44.4)	0.48	
>45	30 (55.6)	0.35	
Fisher grade			0.001*
≤2	3 (5.6)	0.12	
>2	51 (94.4)	0.43	
HH grade			0.557
≤2	9 (16.7)	0.34	
>2	45 (83.3)	0.42	
GCS score			0.016*
<13	35 (64.8)	0.32	
≥13	19 (35.2)	0.56	
Aneurysm treatment			0.948
Coil	35 (64.8)	0.40	
Clip	19 (35.2)	0.41	
Ophthalmological intervention			0.035*
Not performed	28 (51.9)	0.31	
Performed	26 (48.1)	0.51	
Intraocular hemorrhagic type			0.01*
Vitreous hemorrhage	38 (70.4)	0.49	
Retinal hemorrhage	12 (22.2)	0.25	
Mixed	4 (7.4)	0.05	
Ophthalmologic examination onset (days)			0.566
≤7	13 (24.1)	0.46	
>7	41 (75.9)	0.39	

DVAR, the degree of visual acuity recovery; HH, Hunt and Hess; GCS, Glasgow coma scale.
Values are presented as number (%).
*$P<0.05$.

and the location and orientation of an aneurysm were also investigated. The mean DVAR was 0.4 in our study. Statistical analysis revealed significant difference in DVAR in terms of sex (male vs. female; $P=0.001$), GCS score (<13 vs. ≥13; $P=0.016$), Fisher grade (≤2 vs. >2; $P=0.001$), ophthalmologic intervention (not performed vs. performed; $P=0.035$), and type of ophthalmological hemorrhage (vitreous vs. retinal vs. mixed; $P=0.01$). There was no statistical correlation regarding onset time of ophthalmological examination (≤7 days vs. >7 days; $P=0.566$) (Table 2).

Locations of aneurysm were distributed in 19 cases (35.2%) with anterior communicating artery (ACoA), 9 cases (16.7%) with middle cerebral artery (MCA), 9 cases (16.7%) with posterior communicating artery (PCoA), 5 cases (9.3%) with internal carotid artery (ICA), and 8 cases (14.8%) with vertebral artery. Orientations of the aneurysm were followed as 17 cases (31.5%) with superior direction, 14 cases (25.9%) with anterior direction, and 13 cases (24.1%) with posterior direction (Fig. 1). The location of the aneurysm was divided into anterior and posterior circulation. The anterior circulation included ACoA, MCA, PCoA, anterior choroidal artery, and ICA. The orientation of the aneurysm was divided into anterior and other directions. The incidence for the location of the aneurysm was high in the anterior circulation (83.3%), but there was no significant difference compared with DVAR of posterior circulation ($P=0.207$). Analysis of orientation of the aneu-

Table 3. Location and orientation of aneurysms in 54 eyes

Characteristics	No. of eyes	Mean DVAR	P value
Location of aneurysm			0.207
Anterior circulation*	45 (83.3)	0.38	
Posterior circulation†	9 (16.7)	0.54	
Orientation of the aneurysm			0.034‡
Anterior	14 (25.9)	0.58	
Others	40 (74.1)	0.35	

DVAR, the degree of visual acuity recovery.
*Anterior communicating artery, middle cerebral artery, posterior communicating artery, anterior choroidal artery, and internal carotid artery.
†Vertebral artery and posterior inferior cerebellar artery.
‡$P<0.05$.

rysm exhibited a statistically significant difference in DVAR about anterior orientation (anterior orientation vs. other orientation; P=0.034) (Table 3).

The favorable recovery group with DVAR greater than 0.4 showed statistical significance in sex (P=0.001), GCS score (P=0.002), orientation of aneurysm (P=0.037), and ophthalmological intervention (P=0.015). But, no statistical significance was observed between the DVAR and factors such as HH grade (P=0.804), surgical treatment of the aneurysm (P=0.465), intraocular hemorrhagic type (P=0.065), and location of the aneurysm (P=0.461) (Table 4).

Multivariate logistic regression analysis of these pa-

Table 4. Comparison of characteristics between unfavorable and favorable visual recovery group

Characteristics	Unfavorable recovery* No. of eyes	Favorable recovery[†] No. of eyes	P value
Mean age	45.9±8.4	42.1±6.9	0.083
Sex (male)	12 (37.5)	19 (86.4)	0.001[‡]
Fisher grade			0.262
≤2	3 (9.4)	0	
>2	29 (90.6)	22 (100)	
HH grade			0.804
≤2	5 (15.6)	4 (18.2)	
>2	27 (84.4)	18 (81.8)	
GCS score			0.002[‡]
<13	26 (81.3)	9 (40.9)	
≥13	6 (18.8)	13 (59.1)	
Location of aneurysm			0.461
Anterior circulation	28 (87.5)	17 (77.3)	
Posterior circulation	4 (12.5)	5 (22.7)	
Orientation of the aneurysm			0.037[‡]
Anterior	5 (15.6)	9 (40.9)	
Others	27 (84.4)	13 (59.1)	
Hydrocephalus	12 (50)	12 (50)	0.215
ICH	18 (69.2)	8 (30.8)	0.151
Aneurysm treatment			0.465
Coil	22 (68.8)	13 (59.1)	
Clip	10 (31.3)	9 (40.9)	
Mean time of ophthalmologic examination (days)	67.8±149.9	49.1±85.4	0.6
Intraocular hemorrhagic type			0.065
Vitreous hemorrhage	18 (56.3)	20 (90.9)	
Retinal hemorrhage	10 (31.3)	2 (9.1)	
Mixed	4 (12.5)	0	
Ophthalmological intervention			0.015[‡]
Not performed	21 (65.6)	7 (31.8)	
Performed	11 (34.4)	15 (68.2)	

HH, Hunt and Hess; GCS, Glasgow coma scale; ICH, intracranial hemorrhage.
Values are presented as mean±standard deviation or number (%) unless otherwise indicated.
*DVAR≤0.4.
[†]DVAR>0.4.
[‡]P<0.05.

Table 5. Multivariate logistic regression analysis of factors for influencing favorable recovery (DVAR>0.4)

	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Sex (male)	0.154 (0.079–0.232)	0.001*	9.530 (1.824–49.801)	0.008*
GCS score ≥13	0.132 (0.039–0.215)	0.002*	8.073 (1.226–53.148)	0.030*
Anterior orientation	0.068 (0.002–0.140)	0.037*	5.006 (1.842–29.751)	0.017*
Ophthalmological intervention	0.329 (0.086–0.575)	0.015*	1.567 (0.404–6.083)	0.516

DVAR, the degree of visual acuity recovery; OR, odds ratio; CI, confidence interval; GCS Glasgow coma scale.
*$P<0.05$.

rameters identified statistical significance for male (df=1, P=0.008), GCS score (≥13) (df=1, P=0.03), and anterior orientation of aneurysm (df=1, P=0.017) (Table 5).

DISCUSSION

TS has been referred to the occurrence of vitreous hemorrhage in patients with SAH secondary to a ruptured aneurysm however, it has been only rarely described in association with subdural hematomas or traumatic SAH.[9-11] It is most frequently reported with aneurysm of the anterior circulation, particularly of ACoA and ICA origin.[10-13] In our report, ACoA (35.2%) exhibited the highest frequency showing similarity in results with other studies, but it was not statistically significant with respect to the location of the aneurysm (anterior circulation vs. posterior circulation; P=0.207). Variations have been observed in the incidence of Terson hemorrhage among published studies.[3,12,14-16] The incidence has been reported to range between 2.6 and 27% in patients suffering from aneurysmal SAH.[6,14,15,17,18] In our current study, 23.4% of our patients developed TS.

The intraocular hemorrhage observed in TS is usually bilateral; however, it can be asymmetrical in nature.[12] The first attempt to explain TS suggested that blood crosses the subarachnoid space into its continuation within the optic nerve sheath. It was thought that blood was driven through the sclera in the porous region where the optic nerve enters the globe, and finally appears in the vitreous space within the eyes.[19]

The prognosis of aneurysmal SAH patients with TS has been reported to be poor. Many studies have reported high mortality rate in patients with TS compared to patients without TS.[1,12,16] However, the outcome of visual recovery in surviving patients with aneurysmal SAH has been reported to be good and most of the vitreous hemorrhage has been reported to be cleared spontaneously within months.[11,12,20] However, in our study, the statistically significant difference for DVAR was demonstrated in males, higher GCS score, and aneurysm of anterior orientation. There was little information about the visual recovery according to the orientation of an aneurysm in previous research, but we identified that DVAR was excellent in TS patients with aneurysm of anterior orientation compared to others (P=0.037). It was considered that ophthalmologic problems were detected at an early stage by ophthalmologic examination in patients with higher GCS, and visual acuity improved through active treatment such as intervention. The orientation of the aneurysm is difficult to explain because there is no known mechanism until date.

In our series, the ophthalmological interventions including TPPV, intra-vitreous Avastin injection or laser photocoagulation were performed in 26 eyes (48.1%). The patients undergoing ophthalmological intervention showed statistical significance compared to those who did not (not performed vs. performed; P=0.035), and the DVAR of 0.4 or more was present in the favorable recovery group. Czorlich et al.[21] reported that early TPPV for vitreous hemorrhage contributed to improve best-corrected visual acuity and support neurological rehabilitation. In our study, DVAR of aneurysmal SAH patients having ophthalmological examination within a week was similar to the DVAR of aneurysmal SAH patients undergoing ophthalmological examination a week later, and there was no statistical correlation (P=0.566).

The ophthalmologists have difficulty in diagnosing intraocular hemorrhage immediately because there of the

limitation from mydriasis depending on the patient`s neurological condition. Due to the difficulty in evaluating and making prompt diagnosis, TS is underestimated and its diagnosis can be easily missed. Koskela et al. demonstrated that conventional CT scan has high specificity for detecting TS.[22] In our study, CT scan findings were in accordance with the ophthalmological examination in 24 eyes (44.4%), not in accordance with the ophthalmological examination in 23 eyes (42.6%), and cannot detect ocular hemorrhage in 7 eyes (13%).

This study has several limitations. First, the number of subjects was small. In about 76% of cases, the visual acuity test was performed late (from the 7th day to the 117th day after admission). The late diagnosis of TS did not take into account the risk of hemorrhage such as coagulopathy or taking antiplatelet agents. In future, further study on the mechanism of visual improvement in the anterior orientation of the aneurysm is required.

CONCLUSION

It was observed that TS occurred in about 23.4% of patients with aneurysmal SAH in our study. The DVAR was higher in the aneurysm of anterior orientation, although the location of an aneurysm was not related to the DVAR. The type of intraocular hemorrhage has no correlation with visual recovery. Also, analysis of favorable visual recovery exhibited the statistically significant difference in male, higher GCS score, and anterior orientation of an aneurysm. Patients with vitreous hemorrhage among intraocular hemorrhage types had the greatest DVAR. It is proposed that more active ophthalmological evaluation and treatment can be helpful in contributing to rise the quality of life and improving vision.

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