Brief Report

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# Clinical features of Barré-Lièou syndrome and efficacy of trazodone for its treatment: A retrospective single center study

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**SUMMARY** Barré-Lièou syndrome (BLS) is a manifestation of various autonomic and secondary symptoms including muscle stiffness, tinnitus, dizziness, and pain in various body parts. Although considered to be caused by hyperactivation of the autonomic nervous system due to trauma, there is currently no firmly established etiology or evidence on the treatment and clinical features of BLS. We retrospectively examined the clinical features of BLS and evaluated the efficacy of trazodone (TZD) for its treatment. We conducted a retrospective analysis of the data of 20 consecutive cases with suspected BLS who were treated in our hospital between 2016 and 2019. BLS symptoms were rated on a 10-point scale, and two groups were defined, that is, a mild-BLS group (BLS scores, 1-5) and a severe-BLS group (BLS scores, 6-10). Univariate analysis of patient factors was performed. The BLS score was 6.0 ± 1.7, and the maximum TZD dose was 80 ± 34 mg/day; nine patients (45%) were TZD free, and no TZD side effects were observed, while all patients had a good clinical outcome. There were significant differences between the mild-BLS and severe-BLS groups in the period from injury to diagnosis ($p = 0.015$), chest/back pain ($p < 0.001$), constipation ($p = 0.001$), and maximum TZD dose ($p = 0.008$). BLS involves posttraumatic autonomic symptoms accompanied by depression and insomnia. The sympathetic hypersensitivity theory could explain its etiology. TZD could effectively and safely treat BLS, and early diagnosis and treatment can contribute toward good clinical outcomes. Enhanced recognition and understanding of this disease are warranted.

***Keywords*** Nonspecific symptoms, posttraumatic autonomic symptoms, hyperactivation

## 1. Introduction

Barré-Lièou syndrome (BLS) (*1-3*) is a manifestation of various autonomic and secondary symptoms, such as muscle stiffness, tinnitus, dizziness, and pain in the head, neck, eyes, throat, ears, chest, and back. The symptoms are as follows: 1) inner ear symptoms: dizziness, tinnitus, and feelings of obstruction of the ear; 2) eye symptoms: blurred vision, fatigue, discomfort, and sight loss (asthenopia); 3) chest and back symptoms: chest pain, back pain, arrhythmia, and respiratory distress; 4) pharyngeal and laryngeal symptoms: hoarseness, discomfort in the throat, and swallowing difficulty; 5) head and neck symptoms: headache, sense of head weight, and back of neck pain; 6) others: upper limb and whole body fatigue, upper limb numbness, distraction; 7) secondary psychiatric symptoms (anxiety, depression, and others), and 8) insomnia (*3*).

Although considered to be caused by hyperactivation of the autonomic nervous system due to trauma, there is currently no firmly established etiology. This and the nonspecific nature of many of its symptoms present a challenge both for clinicians, who must provide a correct diagnosis, and for patients, who are often misdiagnosed or face undue scrutiny from insurance companies. To date, there is no established evidence on the treatment and clinical features of BLS (*1-3*). We retrospectively investigated the clinical features of BLS and evaluated the efficacy of trazodone (TZD) for its treatment aiming to contribute novel evidence toward uncovering the nature of this obscure syndrome and provide viable treatment solutions.

## 2. Materials and Methods

This was a single-center retrospective cohort study,

enrolling 20 consecutive patients treated in our hospital between 2016 and 2019, with no positive traumatic changes on head and neck computed tomography or magnetic resonance imaging. They were suspected to have BLS based on the presence of posttraumatic autonomic symptoms. Although there are no specific diagnostic criteria for BLS, the following were adopted (*1-3*): autonomic symptoms observed after trauma, no significant traumatic changes observed on imaging, and improved symptoms through symptomatic blockade treatment. TZD was started at 20 mg/day and increased as needed in all cases where BLS was suspected. Combined use of stellate ganglion block was also considered.

To evaluate the severity of BLS, we calculated a "BLS score" as follows. Autonomic symptoms by organ (head, neck, eyes, ears, throat, chest and back, constipation, others), depression, and insomnia were assigned 1 point each, thus constituting the BLS score (range, 0-10). "Others" included upper limb numbness. TZD was discontinued in patients with a BLS score of 0 (TZD-free). The BLS score (after TZD) was also assessed at the last follow-up. When the BLS score improved by 2 points or more and the condition did not interfere with daily life, we considered that the patient had a good clinical outcome; otherwise, the outcome was considered poor.

Study parameters included age, sex, type of injury (whether or not the patient had been involved in a traffic accident), period from injury to diagnosis, follow-up duration, duration of TZD treatment, history of visiting other departments, presence or absence of autonomic symptoms and depression or insomnia, maximum TZD dose, whether or not TZD could be discontinued (TZD-free), presence or absence of TZD side effects, presence or absence of concomitant stellate ganglion block, and clinical outcome. The effective factors for TZD treatment were also investigated between initial mild (BLS score: 1-5) and severe groups (BLS score: 6-10).

The variables are expressed as percentage values or mean ± standard deviation. Fisher's exact test was used for categorical variables, and the Mann-Whitney U test was used for continuous variables. A $p$ value < 0.05 was considered statistically significant. This study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patients for participation in the study and publication of these cases and the accompanying images. The study design was approved by the appropriate ethics review board of our hospital.

## 3. Results and Discussion

Table 1 shows the clinical features of all 20 cases. The mean (± SD) age was 61.5 ± 13.6 years; there were 8 men and 12 women, and 16 patients (80%) had been injured in car accidents. The period from injury to diagnosis was 25.7 ± 62.8 months, the follow-up duration was 16.6 ± 8.4 months, the duration of TZD treatment was 12.0 ± 3.8 months, and other departments had been visited by 16 patients (80%). The initial BLS score was 6.0 ± 1.7, BLS score (after TZD) was 0.9 ± 1.0, the maximum dose of TZD was 80 ± 34 mg/day, 9 patients (45%) were TZD free, and no TZD side effects (especially

**Table 1. The characteristics of the 20 consecutive cases of suspected Barré-Lièou Syndrome**

| Case No. | Age (years) | Sex | Type of injury (car accident) | Period from injury to diagnosis (days) | Observation period (months) | Duration of TZD treatment (months) | History of visiting other departments | BLS score | BLS score (after TZD) | TZD (max dose, mg) | TZD free | Stellate ganglion block |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 68 | Female | + | 270 | 37 | 12 | + | 9 | 0 | 100 | + | - |
| 2 | 44 | Male | + | 120 | 28 | 11 | + | 5 | 0 | 100 | + | - |
| 3 | 70 | Female | + | 4 | 27 | 16 | + | 5 | 0 | 50 | + | - |
| 4 | 40 | Female | + | 1 | 26 | 17 | + | 7 | 0 | 100 | + | - |
| 5 | 66 | Female | + | 6 | 23 | 17 | + | 5 | 0 | 100 | + | - |
| 6 | 46 | Male | + | 31 | 21 | 21 | + | 9 | 3 | 150 | - | + |
| 7 | 53 | Male | + | 1 | 20 | 12 | + | 4 | 0 | 50 | + | - |
| 8 | 64 | Female | + | 18 | 18 | 10 | + | 7 | 0 | 50 | + | - |
| 9 | 72 | Female | + | 9 | 17 | 11 | - | 6 | 0 | 50 | + | - |
| 10 | 45 | Female | + | 36 | 17 | 16 | + | 6 | 0 | 100 | + | - |
| 11 | 69 | Male | + | 21 | 15 | 15 | - | 8 | 2 | 100 | - | - |
| 12 | 56 | Female | - | 25 | 12 | 12 | + | 7 | 1 | 100 | - | - |
| 13 | 53 | Male | + | 5 | 10 | 10 | + | 8 | 3 | 150 | - | + |
| 14 | 73 | Female | + | 3 | 10 | 10 | + | 5 | 1 | 50 | - | - |
| 15 | 85 | Male | + | 2 | 9 | 9 | + | 4 | 1 | 50 | - | - |
| 16 | 72 | Male | + | 1 | 9 | 9 | - | 4 | 1 | 50 | - | - |
| 17 | 80 | Female | - | 12 | 9 | 9 | + | 7 | 2 | 100 | - | - |
| 18 | 72 | Female | + | 4 | 9 | 9 | - | 4 | 1 | 50 | - | - |
| 19 | 63 | Male | - | 3 | 8 | 8 | + | 4 | 1 | 50 | - | - |
| 20 | 39 | Female | - | 1 | 6 | 6 | + | 5 | 1 | 50 | - | - |

*Abbreviations*. BLS: Barré-Lièou syndrome, n: number of patients, SD: standard deviation, TZD: trazodone.

**Table 2. Differences in patient characteristics and clinical outcomes between the mild and severe groups before trazodone administration**

| Patient factors | BLS score: 1-5 ($n$ = 10) | BLS score: 6-10 ($n$ = 10) | $p$ value |
|---|---|---|---|
| Age, mean ± SD (years) | 63.7 ± 14.3 | 59.3 ± 13.3 | $p > 0.1$* |
| Sex (female), *n* (%) | 5 (50) | 7 (70) | $p > 0.5$† |
| Type of injury (car accident), *n* (%) | 8 (80) | 8 (80) | $p > 0.5$† |
| Period from injury to diagnosis, mean ± SD (days) | 14.5 ± 37.1 | 42.8 ± 80.6 | $p = 0.015$* |
| Follow-up duration (months) | 14.9 ± 8.6 | 18.2 ± 8.3 | $p > 0.1$* |
| Duration of TZD treatment, mean ± SD (months) | 10.7 ± 3.5 | 13.3 ± 3.8 | $p > 0.1$* |
| TZD free, *n* (%) | 4 (40) | 5 (50) | $p > 0.5$† |
| History of visiting other departments, *n* (%) | 8 (80) | 8 (80) | $p > 0.5$† |
| Autonomic symptoms Head, *n* (%) | 9 (90) | 10 (100) | $p > 0.5$† |
| Neck, *n* (%) | 10 (100) | 10 (100) | NA |
| Eyes, *n* (%) | 8 (80) | 7 (70) | $p > 0.5$† |
| Ears, *n* (%) | 4 (40) | 7 (70) | $p > 0.1$† |
| Throat, *n* (%) | 9 (90) | 10 (100) | $p > 0.5$† |
| Chest/Back, *n* (%) | 0 (0) | 9 (90) | $p = 0.00001$† |
| Constipation, *n* (%) | 1 (10) | 9 (90) | $p = 0.001$† |
| Others | 0 (0) | 1 (10) | $p > 0.5$† |
| Depression, *n* (%) | 0 (0) | 3 (30) | $p > 0.1$† |
| insomnia, *n* (%) | 4 (40) | 8 (80) | $p > 0.1$† |
| TZD max dose, mean ± SD (mg) | 60 ± 21 | 100 ± 33 | $p = 0.008$* |
| Stellate ganglion block, *n* (%) | 0 (0) | 2 (20) | $p > 0.1$† |
| Good clinical outcome, *n* (%) | 10 (100) | 10 (100) | NA |

*Abbreviations*. BLS: Barré-Lièou syndrome, n: number of patients, NA: not applicable, SD: standard deviation, TZD: trazodone. *Note*: †Fisher exact test, *Mann-Whitney *U*-test

cardiac overload as an anticholinergic effect, which is considered a serious side effect; not shown in Table 1) were observed. There was concomitant stellate ganglion block in 2 cases (10%), and all patients had good clinical outcome.

Table 2 shows the comparative results of the univariate analysis for all examined patient factors between the initial mild (BLS score: 1-5, $n$ = 10) and severe (BLS score: 6-10, $n$ = 10) groups. There were significant differences between the mild group (BLS scores, 1-5) and severe group (BLS scores, 6-10) for the period from injury to diagnosis (14.5 ± 37.1 *vs*. 42.8 ± 80.6, $p = 0.015$), chest/back pain (0 [0%] *vs*. 9 [90%], $p < 0.001$), constipation (1 [10%] *vs*. 9 [90%], $p = 0.001$), and maximum TZD dose (60 ± 21 *vs*. 100 ± 33, $p = 0.008$). There were no significant differences in other patient factors.

This study showed the efficacy and safety of TZD for the treatment of BLS. Furthermore, the fact that TZD, an oral sympathetic nervous system blocker, was effective, supports the cervical sympathetic hyperactivity theory for the etiology of BLS (*1-6*), that is, posttraumatic cervical sympathetic hypersensitivity could cause BLS. In addition, it provides evidence for the validity of our BLS diagnostic criteria.

Treatment for BLS is supposed to follow the treatment protocol for cervical sprains, but a stellate ganglion block (one of the cervical sympathetic ganglia) or an α-blocker (a sympatholytic drug) is recommended. In addition, various treatments such as neck epidural block, intravenous drip infusion of prostaglandin E1, and acupuncture are performed, but a clear treatment effect has not been obtained and there have been numerous reported refractory cases (*2,3*).

TZD (*7-10*) is an antidepressant used worldwide as a 5-hydroxytryptamine and alpha 1-adrenergic receptor antagonist and serotonin reuptake inhibitor (7). The alpha-blocking effect of TZD is thought to be responsible for symptomatic improvement in patients with BLS (*3*) and paroxysmal sympathetic hyperactivity (*9,10*), which is considered to be a condition similar to sympathetic hyperactivity. TZD, which is commonly used to treat depression because of the mechanism associated with alpha-adrenergic receptor inhibition (*8*), was additionally effective for symptomatic amelioration in BLS (7-*10*).

TZD is relatively safe for use in the elderly, with fewer reported cases of its side effects (*8*). In our study, no patients experienced serious side effects of cardiac overload, and some of the minor side effects of TZD, such as constipation and dizziness showed early improvement.

The results presented in Table 2 suggest that delay in diagnosis could worsen BLS severity. Interestingly, symptoms of chest/back pain and constipation were significantly more frequent in the severe-BLS group than in the mild-BLS group, and the severe-BLS group received, on average, a significantly higher maximum dose of TZD compared to the mild-BLS group. However, when administered at appropriate doses, TZD could eventually be discontinued, and the clinical outcomes were good in both groups.

Because this syndrome presents with autonomic and psychiatric symptoms, insomnia, and others, it is treated as an undetermined complaint, and a physician unfamiliar with the disease cannot establish

a definitive diagnosis (*3-6*). As mentioned above, BLS' pathophysiology has not been established, and thus has not been internationally recognized as an independent syndrome. In the clinical setting, BLS can be diagnosed as a tension-type headache, cervical arm syndrome, traumatic cervical syndrome, or autonomic imbalance (*3,4*). As the mechanisms of these conditions remain undetermined, BLS could be considered when they manifest. In Japan, BLS is not widely recognized by either neurosurgeons or physicians involved in trauma care. In our study, the high percentage (80%) of patients with history of visiting other departments suggested that low awareness of this disease might be a contributing factor to the delay in diagnosis. Clinicians involved in trauma care should understand the pathology and clinical features of the disease and encourage the active use of TZD when BLS is suspected. Based on our findings, early BLS diagnosis and treatment with TZD, based on our diagnostic criteria and BLS score, could contribute toward a good clinical outcome for patients.

Our study has some limitations. This study involved selection bias due to its retrospective nature. As this retrospective study included a relatively small sample size, future prospective studies with a larger number of cases are suggested to confirm our findings.

In conclusion, BLS involves posttraumatic autonomic symptoms and may be accompanied by depression and insomnia. This study provided evidence supporting the sympathetic hypersensitivity theory to explain the etiology of BLS. TZD was shown to be safe and effective for BLS treatment. Severe BLS is often accompanied by chest/back pain and constipation, but early diagnosis and treatment can contribute toward good clinical outcomes. Enhanced recognition and understanding of this disease by physicians and society are warranted.

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**References**

1. Li Y, Peng B. Pathogenesis, diagnosis, and treatment of cervical vertigo. Pain Physician. 2015; 18:E583-595.
2. Ishikawa S, Katayama D, Takahara H, Kojo S, Moriyama E, Hashimoto H. Epidural blood patch as a successful treatment of Barrè-Lièou syndrome: report of two cases. Masui. 2003; 52:1305-1311.
3. Morinaga Y, Nii K, Sakamoto K, Inoue R, Mitsutake T, Hanada H. Focus on diagnosis, treatment, and problems of Barré-Lièou syndrome: Two case reports. Drug Discov Ther. 2019; 13:239-243.
4. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E. Scientific monograph of the Quebec task force on whiplash-associated disorders: redefining "whiplash" and its management. Spine (Phila Pa 1976). 1995; 20:1S-73S.
5. Pearce JM. Barré-Liéou "syndrome". J Neurol Neurosurg Psychiatry. 2004; 75:319.
6. Foster CA, Jabbour P. Barré-Liéou syndrome and the problem of the obsolete eponym. J Laryngol Otol. 2007; 121:680-683.
7. Saenz de Tejada I, Ware JC, Blanco R, Pittard JT, Nadig PW, Azadzoi KM, Krane RJ, Goldstein I. Pathophysiology of prolonged penile erection associated with trazodone use. J Urol. 1991; 145:60-64.
8. Yamada H, Kikuchi R, Katayama J, Nakamura A, Miyazaki H. Paroxysmal sympathetic hyperactivity after surgery for cerebral hemorrhagic arteriovenous malformation: a case report. J Stroke Cerebrovasc Dis. 2018; 27:2768-2769.
9. Morinaga Y, Nii K, Hanada H, Sakamoto K, Inoue R, Mitsutake T. Efficacy of trazodone for treating paroxysmal sympathetic hyperactivity presenting after left temporal subcortical hemorrhage. Intractable Rare Dis Res. 2020; 9:119-122.
10. Morinaga Y, Nii K, Sakamoto K, Inoue R, Mitsutake T, Hanada H. Efficacy of trazodone for treating paroxysmal sympathetic hyperactivity presenting after thalamic hemorrhage: A case report. Drug Discov Ther. 2019; 13:168-171.

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