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## **Posner-Schlossman Syndrome in Wenzhou, China: a retrospective review study**

Running head: Incidence of Posner-Schlossman Syndrome in Wenzhou

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## **Synopsis**

This study reports a relatively high frequency of Posner-Schlossman Syndrome in south-east China and its general characteristics.

**ABSTRACT**

**PURPOSE:** To describe the incidence of Posner-Schlossman syndrome (PSS) in Lucheng District, Wenzhou, China, over a 10-year period.

**METHODS:** We reviewed retrospectively the medical records of all inpatient and outpatient patients diagnosed with PSS during the years 2005-2014 in the Eye Hospital of Wenzhou Medical University. The keywords of 'glaucomatocyclitic crisis', 'Posner-Schlossman syndrome' and 'PSS' were used for the retrieval. Only patients with registered residing address in Lucheng District where the hospital located were finally selected. The cumulative incidence and annual incidence of PSS were calculated based on the sum of household registered population and temporary resident population in Lucheng District.

**RESULTS:** A total of 576 patients with PSS (339 males and 237 females) met the retrieval criteria. The mean age of these subjects at the first clinic visit was  $40\pm 15$  years. Intraocular pressure (IOP) of the initial record was  $31.91\pm 15.37$  mm Hg. The 10-year cumulative incidence of PSS in Lucheng district was 39.53 per 100,000 population, while the mean annual incidence of PSS in this area was 3.91 per 100,000 population. Majority of these patients were 20-59 years old (83.9%). Males showed a significantly higher cumulative incidence of PSS than females ( $P=0.010$ ). Higher rate of newly onset cases was found in spring (31%) than in other seasons ( $P=0.006$ ).

**CONCLUSIONS:** Our results suggest a relatively high incidence of PSS in Wenzhou, a southeastern city in China. Young, male adults are prone to be affected in spring. However, the etiology and other risk factors are still waited to be clarified.

**Keywords:** Epidemiology, Intraocular pressure, Inflammation

**Introduction**

Posner-Schlossman syndrome (PSS), also known as glaucomatocyclitic crisis, is first delineated by Posner and Schlossman in 1948.[1] It is usually characterized by unilateral recurrent episodes of acute elevated intraocular pressure (IOP) accompanied by mild anterior chamber inflammation or fine white keratic precipitates (KP).[2] PSS is typically self-limited without sequelae and may be alleviated by anti-hypertensive and anti-inflammatory agents. Repeated attacks may lead to long-term glaucomatous optic nerve damage over 5 to 10 years after the first onset.[3 4] Several factors such as viral infection, autoimmune, autonomic dysregulation, vascular endothelial dysfunction, and allergic conditions have been proposed as possible contributors to the development of this disease.[4-9] However, the exact etiology and pathophysiology are still not fully understood, which makes it difficult to prevent the recurrence as well as the secondary optic nerve damage of the patient.[3 4]

PSS is commonly perceived as a rare condition. Minimal discomfort despite marked and acute elevation of pressure lead to an under-detection of the disease. It is hard to collect the epidemiological data of PSS through epidemiological survey. Although the proportion of PSS among uveitis had been reported [10-12] since it was first discovered, extremely limited information is available regarding the epidemiology of PSS. A brief introduction of the population statistics of PSS came from Paivonsalo-Hietanen's work in 1997, which reported an incidence of 0.4 and prevalence of 1.9/100,000 of PSS in Finland.[13] Lack of epidemiological data makes it difficult to evaluate the disease related health care decision-making and planning at population level. In present study, we retrospectively reviewed the medical records in a tertiary eye center in Wenzhou, a coast city in the South-East China, during a 10-year period (2005–2014). The incidence of PSS and its general characteristics were described.

## **Methods**

### ***Population and procedures***

Clinical records in the electronic medical record system (Thiseye, Eye Care System, Versions 15.11.26.2011) of the Eye Hospital of Wenzhou Medical University were surveyed from January 1, 2005, through December 31, 2014. This tertiary eye hospital is one of the TOP 5 eye centers in China with more than 500,000 annual out-patient

visits. Due to demographic convenience and highly-recognized reputation of the hospital, the majority of the patients with eye diseases in the Lucheng district, where the hospital located, presented and were treated at this center. Therefore, the hospital record analysis provided a relatively complete collection of cases in this district. This study adhered to the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the Wenzhou Medical University. As this was a retrospective study with de-identified data informed consent was not required.

We used the keywords ‘glaucomatocyclitic crises’ or ‘Posner-Schlossman syndrome’ or ‘PSS’ for the retrieval process. Both out-patient and in-patients clinics were included. Diseases other than PSS but contained some of the same Chinese characters with PSS were excluded. Duplicated records for the same patients were removed. Patients with registered residence in Lucheng District were selected for further calculation and analysis of the cumulative, as well as the annual incidence of PSS. Data retrieve was performed twice by two independent investigators and the consistence between two retrieve were evaluated. Discrepant records were re-searched by a third investigator until consensus was obtained from all these three investigators. Information including age, gender, time of the first visit, intraocular pressure was recorded.

### ***Diagnosis and Definitions***

Posner-Schlossman syndrome may mimic a variety of ocular disorders. Diagnosis of PSS is inherently difficult. To confirm the accuracy of the diagnosis, a questionnaire on diagnosis criteria of PSS was filled by 46 clinical ophthalmologists working in the hospital on December 9, 2015. The most frequently selected answers were: (1) unilateral transient episode of elevated IOP with blurred vision; (2) mild anterior chamber inflammation and/or a few small-to-medium, discrete, round, white keratic precipitates accumulating in the lower half of the cornea, no iris posterior synechia; (3) deep anterior chamber with wide and open angle; (4) Recurrent attack with varied frequency.

### ***Data and Statistical analysis***

In order to eliminate the influence of population mobility, the cumulative incidence and annual incidence (per 100,000 population) of PSS were calculated based on the sum of household registered population and temporary resident population in Lucheng district in present study. The population figures were obtained from the Zhejiang Provincial Bureau of Statistics (Zhejiang Statistical Yearbook 2005-2014).

The gender distribution of this population in 10-year intervals were also counted from the population statistics to calculate the cumulative incidence and the annual incidence in different gender groups.

All analyses were performed with SPSS software (version 20.0, SPSS Inc. Chicago, Illinois, USA). Chi-square test was used to compare the incidence and cumulative incidence between different demographic groups. A p value less than 0.05 was considered statistically significant.

### **Results**

A total of 2286 PSS patients were retrieved from the electronic medical record system from January 1, 2005, through December 31, 2014 (1398 males and 888 female with a mean age of  $38.4\pm 13.8$ ). Among all these PSS patients, 576 subjects were registered as residences of Lucheng District (339 males and 237 females). The mean age at the first clinic visit was  $40\pm 15$  years (ranged from 10 to 81 years). IOP of initial record (with or without IOP-lowering agents) was  $31.91\pm 15.37$  mm Hg (ranged from 7.0 to 59.4 mm Hg), 83.0% patients had a presenting IOP that was greater than 21 mmHg with or without IOP medications, 73.5% patients had an presenting IOP that was greater than 30 mmHg and 54.6% patients had an presenting IOP that was greater than 40 mmHg. During 2005 to 2014, 75.5% patients had visited the hospital for treatment at least twice. 51.2% patients with had duration of PSS for more than 2 years (from 2 to 10 years) and 24.3% patients experienced 2 or more visit (from 2 to 12 times) in one year.

During 2005 to 2014, the population in Lucheng district fluctuate between 1.35 million to 1.56 million, with a little bit majority of male. The cumulative incidence of PSS in this district was 39.53 (95% CI: 36.30-42.76) per 100,000 population over 10 years. The mean annual incidence of PSS was 3.91 per 100,000 population. The overall incidence rate increased from 3.66 per 100,000 person in 2005 to 4.44 in 2014 ( $P<0.027$ ; Figure 1).

The cumulative incidence of PSS in male and female was 43.47 (95% CI: 38.84–48.09) per 100,000 and 35.00 (95% CI: 30.54–39.54) per 100,000, respectively. Males showed a significantly higher cumulative incidence of PSS than females ( $P=0.010$ ). The mean annual incidence was 4.33 per 100,000 for male and 3.34 per 100,000 for female. Annual incidence of PSS in female rise from 3.35 (95% CI, 1.95–4.75) per 100,000 person-years in 2005 to 4.82 (95% CI, 3.13–6.52) in 2014 ( $P<0.014$ ; Figure

1), while in males the incidence remained stable over 10 years. During the 10-year observation, males consistently showed a higher incidence of PSS than females, although the difference reached statistically significant only in 2008 and 2009 (Table 1).



**Table 1. Incidence of PSS per 100,000 population in year 2005-2014.**

years	Overall			Male		Female		$\chi^2$	P
	N	Incidence (95%CI)	n	Incidence (95%CI)	n	Incidence (95%CI)			
2005	54	3.66 (2.68, 4.64)	32	3.91 (2.55, 5.26)	22	3.35 (1.95, 4.75)	0.310	0.578	
2006	51	3.54 (2.57, 4.52)	30	3.84 (2.46, 5.21)	21	3.19 (1.83, 4.56)	0.414	0.520	
2007	48	3.29 (2.36, 4.22)	31	3.92 (2.54, 5.30)	17	2.54 (1.33, 3.75)	2.112	0.146	
2008	58	3.87 (2.87, 4.86)	39	4.82 (3.31, 6.34)	19	2.75 (1.51, 3.98)	4.156	0.041	
2009	43	2.99 (2.10, 3.88)	32	4.18 (2.73, 5.62)	11	1.64 (0.67, 2.60)	7.721	0.005	
2010	70	4.84 (3.71, 5.97)	38	4.94 (3.37, 6.52)	32	4.72 (3.08, 6.35)	0.038	0.846	
2011	62	3.97 (2.98, 4.95)	34	4.08 (2.71, 5.45)	28	3.84 (2.42, 5.26)	0.057	0.811	
2012	70	4.84 (3.71, 5.97)	38	5.00 (3.41, 6.60)	32	4.66 (3.04, 6.27)	0.089	0.765	
2013	60	4.13 (3.09, 5.18)	36	4.71 (3.17, 6.25)	24	3.49 (2.09, 4.89)	1.301	0.254	
2014	60	4.44 (3.32, 5.57)	29	4.10 (2.61, 5.59)	31	4.82 (3.13, 6.52)	0.399	0.528	

CI=confidence interval

Majority of these patients were 20-59 years old (83.9%). A considerable population older than 60 years (12.0%), even over 70 years (3.5%) was also observed (Table 2).

**Table 2. The descriptive summary of patients with PSS by age and gender.**

Age(year)	Male		Female		Total	
	No.	%	No.	%	No.	%
<20	15	4.5	9	3.8	24	4.1
20-29	77	22.7	60	25.3	137	23.8
30-39	92	27.1	69	29.1	161	28.0
40-49	70	20.6	36	15.2	106	18.4
50-59	43	12.7	36	15.2	79	13.7
60-69	29	8.6	20	8.4	49	8.5
≥70	13	3.8	7	3.0	20	3.5
Total	339	100.0	237	100.0	576	100.0

Patients younger than 20 years old accounted for 4.1% of all diagnosed PSS. Taking the season and climate into account, the frequency of the first visit in spring, summer, autumn and winter of these PSS patients was 31.0%, 24.0%, 21.2% and 23.8% (Table 3), respectively. Spring demonstrated a little bit higher onset of PSS than other seasons ( $\chi^2=12.458$ ,  $P=0.006$ ).

**Table 3. The number of newly diagnosed PSS and visits per season**

Season	Number of Newly diagnosed		Number of visits	
	n	%	n	%
Spring(March to May)	179	31.0	1332	29.0
Summer(June to August)	138	24.0	1067	23.3
Autumn(September to November)	122	21.2	1096	23.9
Winter(December to February)	137	23.8	1092	23.8
Total	576	100.0	4587	100.0

## Discussion

In this study we reported a 10-year cumulative incidence of 39.53 per 100,000 and an annual incidence of 3.91 per 100,000 population of PSS in Lucheng district of Wenzhou. To our knowledge, it is the first report about the incidence of PSS in Chinese population. It was prone to affect young adults and middle aged patients between 20-60 years old, but subjects younger than 20 years or older than 60 years were not exempted. Males showed a higher cumulative incidence and incidence of PSS than females.

Epidemiological data of PSS is extremely limited. The only one study looking at the incidence of PSS came from Finland in 1997, which reported an annual incidence

of 0.4 and prevalence of 1.9/100,000 of PSS.[13] The overall uveitis incidence worldwide was 24.9-52.4 cases per 100,000 person-years.[14-16] PSS accounts for 1.8%-6.7% of the uveitis according to different studies.[11 12 17] In the present study, we reported an annual incidence of 3.91 per 100,000 population for PSS in Lucheng district in Wenzhou, about 10 times higher compared to that reported in Finland. To note, although, as mentioned above, the Eye Hospital of Wenzhou Medical University may cover the majority of the patients with eye disease in the Lucheng district in Wenzhou, still some cases had presented to other hospitals in this district, which may, therefore, lead to underestimation of the incidence of PSS. To eliminate this bias, we also retrieved the medical records from the department of Ophthalmology in other four general hospitals in Lucheng district (The First Affiliated Hospital of Wenzhou Medical University; The Second Affiliated Hospital of Wenzhou Medical University; Wenzhou Central Hospital; Wenzhou City Hospital of Traditional Chinese Medicine and Western Medicine Combined) in addition to the Eye Hospital of Wenzhou Medical University from 2013 to 2015, during which period the electronic medical records were available in all these medical affiliations. When combined the data from these five departments, a higher annual incidence of 4.44 per 100,000 population was obtained. These evidence suggests a higher incidence of PSS in Wenzhou than that reported in Finland and the deduced rate from uveitis.[13]

Previous study [18] has shown that the prevalence of uveitis in Wenzhou (310 per 100,000) is significantly higher than other regions.[19-21] Moreover, Dernouchamps and Nakahara et al reported that Asian PSS have devoted a larger percentage of uveitis than other regions.[10] [11] Underlying mechanisms for this difference is not quite clear. It has been recently reported that gene polymorphisms at the HLA-B and HLA-C loci, especially at HLA-C\*1402, A\*1101~C\*1402 and B\*5101~C\*1402 might predispose to the development of PSS in southern Chinese Han population.[9] Consistently, Hirose and his colleagues reported that HLA-Bw54 showed significant association with PSS in a Japanese population.[7] High frequencies of HLA- A\*11 and B\*51 allele are observed in Chinese population.[22-25] Genomewide association study also revealed more alleles in the HLA-B region in Chinese Han population (44 alleles) than in the Caucasian population (32 alleles).[26] The difference in the incidence of PSS between different reports may due to the gene variability between different ethnicities.

Other factors, including virus infection, diet or other life style, environment, and climate may also contribute to the epidemiological variance of PSS among different

regions. Wenzhou is located at the east coastline of China, the life style and food diet has some specific features not liking other parts of China, especially, the cooking methods for seafood. We have noted that the prevalence of thyroid cancer in Wenzhou is also much higher than that in general population in China.(9.6 per 100,000 population in Wenzhou Vs 1.4 per 100,000 population in China).[27 28]

It has been commonly perceived that PSS typically, or even almost exclusively, affects adults between the ages of 20-50 years.[29-32] PSS in individuals older than 60 years as well as in adolescence is considered as a rare condition. [33-35] In present study, 83.9% of the patients with PSS were between 20 and 60 years. While, a considerable number of patients (12.0%) older than 60 years old were also detected. Although we could not exclude the possibility that some of these older patients may have already been affected with PSS for several years before their first clinical visit, an older age involvement should gain more attention.

Our present study found that the incidence of PSS is significantly higher in males than that in females. Gender predilection in PSS has not been clearly described. The privilege distribution in young adult, male patients of this disease may be related with the endocrine, hormone or immune status. Underlying mechanisms are still waiting to be elucidated.

In present study, we found that the onset and recurrence of PSS was more frequent in spring, a season in which allergic disorders including hay fever, asthma, eczema, severe reactions to insect stings, and plants are also prone to attack. Knox and coauthors[36] reported that 65% patients with PSS had major allergies and 42% of the patients with history of allergy for more than eight years.[37] This season predilection may suggest a correlation between allergy and PSS.

One strength of the current study is the fact that cumulative incidence and incidence of the disease were calculated by the sum of household registered population and temporary resident population. In China, actual population is larger than permanent population due to the influence of population mobility. Thereby, cumulative incidence and incidence of PSS would be overestimated if calculated by permanent population

This study had some inevitable limitations due to the retrospective design. First, although we performed a questionnaire investigation to confirm the diagnostic accuracy, misdiagnose of PSS could not be avoided. We assumed the rate of missed, incorrect or delayed diagnoses was as high as 5% to 15% [38 39] and still get a high annual

incidence of 3.77 to 4.22 per 100,000 (five hospitals) for the PSS. Second, detailed description of the symptoms, signs, and previous history of allergy of the patients could not be obtained through this medical electronic system, which prevent us from getting a full description of the disease. Third, information of regular follow-up is absent. Most of the patients only come to the hospital at his or her first attack or attack with relatively prominent symptoms. Some recurrent patients may be unaware of their diseases due to mild self-perceived symptoms or may be reluctant to see a doctor while using anti-inflammatory drugs themselves instead. It is difficult to draw a clear picture of the nature course of PSS based on present data. The high prevalence of PSS in Wenzhou may provide us an opportunity for the better understanding of this 'rare' condition. We are now performing a prospective study to further confirm the present results and to investigate the clinical characteristics, as well as the mechanisms, of the PSS.

In summary, we describe a high cumulative incidence of PSS in south-east China. Young, male adults are prone to be affected. PSS maybe not as rare as we previously perceived. Good designed prospective studies are in urgent need for better understanding this unique, inflammatory and ultimate optic nerve threaten syndrome.

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Contribution of authors: Involved in design of study (Yuanbo Liang); Conduct of study (Junhong Jiang, Yuanbo Liang); Collection of data (Junhong Jiang, Mali Dai, Yanqian Xie, Cheng Hu); Management (Shaodan Zhang, Yuanbo Liang), analysis (Junhong Jiang, Juanyuan Yang, Guangyun Mao) and interpretation (Junhong Jiang, Shaodan Zhang, Yuanbo Liang) of the data; preparation of the manuscript (Junhong Jiang, Shaodan Zhang, Yuanbo Liang); provision of materials and resources (Yuanbo Liang, Fan Lu); and review and approval of the manuscript (Yuanbo Liang, Fan Lu, Shaodan Zhang).

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**Figure 1. Trends for the incidence in Posner-Schlossman Syndrome over the years 2005-2014 in Lucheng district in Wenzhou, China.**