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Iris Nodules Associated with Uveitis: Comparison between Sarcoidosis and Vogt-Koyanagi-Harada Disease

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Purpose: To clarify the clinical features and the therapeutics of iris nodules associated with uveitis. A comparison was made between sarcoidosis and Vogt-Koyanagi-Harada disease (VKH), in which iris nodules are most frequently observed. **Patients and Methods:** The clinical database of 547 consecutive uveitis patients referred to Tokyo Women's Medical University from July 2003 to October 2004 was retrospectively reviewed. A definitive diagnosis was given in 109 cases (205 eyes) with sarcoidosis and 21 cases (42 eyes) with VKH, and the frequency, onset time, regions, resolving periods, and therapeutics of iris nodules were compared. **Results:** Fifty of 547 patients (9.1%) presented iris nodules. Thirty-seven eyes (18.0%) with sarcoidosis and 13 eyes (31.0%) with VKH had iris nodules. In sarcoidosis, 26 eyes (70.3%) with iris nodules were observed in the first episode of uveitis. On the other hand, all 13 VKH affected eyes with iris nodules were observed on the recurrence ($p < 0.00002$). Resolving periods of iris nodules after the medication were 2.1 ± 0.2 weeks in sarcoidosis and 5.0 ± 1.0 weeks in VKH ($p < 0.02$). Resolving periods of iris nodules in VKH were 9.6 ± 1.4 weeks with topical steroids alone, 5.8 ± 2.0 weeks with systemic steroids, and 2.6 ± 0.6 weeks with periocular steroids injection. **Conclusions:** Although sarcoidosis and VKH are the common granulomatous uveitides in Japan, their onset time, regions of development, duration and therapeutic response of iris nodules differ. Iris nodules developed in these diseases may vary in clinical features and mechanism.

Key Words: iris nodules, sarcoidosis, Vogt-Koyanagi-Harada disease, corticosteroids

Introduction

Iris nodules are inflammatory cell precipitates that lie at the pupillary margin or on the iris surface. These nodules are uncommon clinical signs of uveitis, and could be found in non-granulomatous as well as granulomatous uveitis. The diseases most commonly associated with iris nodules and uveitis include sarcoidosis, Vogt-Koyanagi-Harada disease (VKH), Fuchs' heterochromic iridocyclitis, and infectious uveitis[1)~4)]. Most cases of uveitis with iris nodules can be attributed to non-infectious entities that are generally responsive to immunosuppressive therapy[4)]. The mainstay of non-infectious uveitis treatment is corticosteroids, which are administrated in three forms: topically, locally via sub-Tenon's or intravitreal injection, and systemically[5)]. When inflammation is treated, the nodules will resolve. To provide a detailed description of uveitis and get useful information for diagnosis and treatment, we focused on iris nodules and studied its clinical future and therapeutic responses.

Patients and Methods

Design of this study was a retrospective noncomparative case series. Participants were a total of 547 consecutive uveitis patients referred to the uveitis service at Tokyo Women's Medical University from July 2003 to October 2004. We examined the clinical database to identify cases of uveitis associated with iris nodules. Cases of uveitis with iris nodules affected by sarcoidosis and VKH were further reviewed to study the clinical future of iris nodules; frequency, onset time, regions, duration, and thera-

Table 1 Uveitis associated with iris nodules

Disease	Number of patients (%)
Sarcoidosis	24 (48)
VKH	8 (16)
Herpes	3 (6)
Tuberculosis	3 (6)
Fuchs	1 (2)
Unknown	11 (22)
Total	50 (100)

VKH, Vogt-Koyanagi-Harada disease; Herpes, herpetic iridocyclitis; Fuchs, Fuchs' heterochromic iridocyclitis.

peutic response. The criteria established by the Diffuse Pulmonary Disease Committee of Japan were used to diagnose patients with sarcoidosis[6], and revised diagnostic criteria for VKH were used to diagnose patients with VKH[7]. For the evaluation of response to steroid therapy, these subjects were classified into three groups: the topical group, the periocular group, and the systemic group. The therapeutic principle of uveitis at our department is as follows: topical corticosteroids were given to patients with mild inflammation of anterior segment; periocular corticosteroids injections were given to patients with severe inflammation of anterior and posterior segment; systemic corticosteroids were given to patients of VKH with active fundus findings. Results were expressed as means ± SE. Data were analyzed using χ^2 test, unpaired t-test or one-way analysis of variance (ANOVA) followed by post hoc test. $p<0.05$ was considered statistically significant.

Results

At first, we surveyed the prevalence of uveitis associated with iris nodules. Of a total of 547 uveitis patients, 50 patients (9.1%) presented iris nodules. These 50 patients comprised: sarcoidosis 24 cases (48%) followed by VKH 8 cases (16%), herpetic iridocyclitis 3 cases (6%), tuberculosis 3 cases (6%), Fuchs' heterochromic iridocyclitis 1 case (2%), and unknown cause 11 cases (22%) (Table 1).

In this study, a comparison was made between sarcoidosis and VKH, in which iris nodules were most frequently observed. Of the 547 cases, 205 eyes of 109 patients (average 57.6 ± 16.2 years old) with sarcoidosis (Group S), 42 eyes of 21 patients (average 58.8 ± 15.3 years old) with VKH (Group V), diagnosed according to each criteria, were identified and subjected to the following study.

Iris nodules were observed at least once in 37 eyes (18.0%) in Group S and 13 eyes (31.0%) in Group V. However, there was no significant difference in the frequency between Group S and V. There was also no difference in the frequency between the two groups according to gender and age. Table 2 shows the onsets and regions of iris nodules. Onsets of iris nodules in these diseases were different. In Group S, 26 eyes (70.3%) showed iris nodules in the first episode of uveitis, while Group V showed them only during inflammation recurrence. The difference was statistically significant (χ^2 test, $p = 0.000013$). Because a few eyes repeated recurrence of inflammation, iris nodules were observed 47 times in Group S and 25 times in Group V. In Group V, the nodules had developed only on the pupillary border (i.e. Koeppe nodule), but on neither the iris surface (i.e. Bussaca nodule) nor the anterior chamber angle. In Group S, Koeppe nodule was observed 30 times, Bussaca nodule 7 times, and angle nodule 16 times. Five eyes presented Koeppe and angle nodules at the same time, and one eye presented Bussaca and angle nodules at the same time. The number of iris nodules ranged from 1 to 20 in both sarcoidosis and VKH.

As shown in Table 3, the average resolving periods of iris nodules after medication were 2.1 ± 0.2 weeks in sarcoidosis and 5.0 ± 1.0 weeks in VKH (unpaired t-test, $p = 0.013$). The therapeutic responses of iris nodules were evaluated by the resolving periods of nodules. The durations of iris nodules in Group V were 9.6 ± 1.4 weeks with topical steroids alone, 5.8 ± 2.0 weeks with systemic steroids, and 2.6 ± 0.6 weeks with periocular steroids injection. The duration was significantly shorter in the periocular group than in the topical group (Fischer's Protected Least Significant Difference, $p = 0.045$). In Group S, there was no difference in the duration of iris nodules between the periocular and topical groups. Systemic corticosteroids were not given to any patient in Group S.

Table 2 Onsets and regions of iris nodules

	Group S (n=205 eyes)	Group V (n=42 eyes)
Number of eyes with nodules	37 (18%)	13 (31%)
Onsets of iris nodules*		
First episode	26	0
Recurrence	11	13
Number of onsets with nodules	47 times	25 times
Number of onsets in each region		
Koeppe nodule	30	25
Bussaca nodule	7	0
Angle nodule	16	0

χ^2 test, *p=0.000013.

Table 3 Resolving periods of iris nodules

(weeks)

	Group S	Group V	
Average duration*	2.1±0.2	5.0±1.0	
Topical	2.3±0.25 (n=30)	9.6±1.4 (n=7)	**
Periocular	1.8±0.3 (n=17)	2.6±0.6 (n=5)	**
Systemic	—	5.8±2.0 (n=13)	

*unpaired t-test, p=0.013, **Fischer's PSLD, p=0.045.

Discussion

In our study, 9.1% of uveitis patients presented iris nodules and the most frequent uveitis associated with iris nodules was sarcoidosis, followed by VKH. Myeres et al reported a different diagnosis of iris nodules with uveitis[4], and most cases of uveitis with iris nodules were attributed to non-infectious entities. Indeed, when we combine our results with sarcoidosis and VKH, they accounted for 64% of all iris nodules with uveitis patients. Compared with results from southern Japan[8], the order of most frequently observed uveitis with iris nodules was the same, while our prevalence of uveitis with iris nodules was lower than their report. In the southern Japan report, the prevalence of uveitis with iris nodules was 21% and interestingly, there were 12 eyes of human T-lymphotropic virus type 1 (HTLV-1)-associated uveitis, while we did not have any. The relatively high proportion of HTLV-1-associated uveitis in their report is probably due to a high prevalence of HTLV-1 virus carriers in the southern Japan area[9].

We observed iris nodules in 18.0% of sarcoidosis patients and in 31.0% of VKH patients. Previous reports showed that the frequencies of iris nodules were 11-50% in sarcoidosis[8)10)~14)], and 5-10% in VKH[15)16)]. Our result was within the same range in sarcoidosis, but the frequency of iris nodules in VKH was higher than their report. Iris nodules are an accumulation of inflammatory cells, and Bussaca nodules tend to appear in severe uveitis cases. In our study, all Koeppe, Bussaca, and angle nodules developed in sarcoidosis and they were mainly observed in the first episode of uveitis. On the other hand, iris nodules were observed only on the recurrence of inflammation in VKH and were all Koeppe nodules. Pathologically, VKH is a type of granulomatous panuveitis, but clinically granulomatous ocular manifestations are more commonly observed in the convalescent or recurrent phase than the acute phase. Cho et al reported that Koeppe nodules were found only in VKH cases with chronic and delayed uveitis[17]. They postulate that iris nodules can be an indicator of procrastination in VKH. As Koeppe nodules cause posterior synechiae, and may develop complicated cataract and secondary glaucoma, we need to pay attention to their therapeutics.

Corticosteroids are the mainstay of treatment in both sarcoidosis and VKH. In sarcoidosis, anterior and intermediate or posterior uveitis are usually treated with topical corticosteroids. Systemic corticosteroids are indicated in uveitis not responding to topical corticosteroids therapy or in the presence of severe posterior involvement. The key to successful therapy for VKH is early and aggressive treatment

with corticosteroids. This may result in fewer complications and less likelihood of recurrence of the disease in the future. Patients who fail to respond to steroid therapy or develop intolerable adverse effects may require immunomodulatory therapy. Few reports focused on the therapeutic response to iris nodules in these diseases[17)~20)]. In our study, the average duration of iris nodules in VKH was significantly longer than that of sarcoidosis. Moreover, the duration of iris nodules in VKH had been markedly shortened by periocular corticosteroids injection. Although the therapeutic principles in usage of corticosteroids vary among institutions, and we individualize treatment for each particular patient, the cases with sarcoid uveitis treated at our institution did not require systemic corticosteroids and achieved the desired control. Furthermore, none of the sarcoidosis and VKH patients at our institution required immunomodulatory drugs.

Sarcoidosis is a multisystem inflammatory disease of unknown etiology. The hallmark of the disease is the noncaseating granuloma. Histologically, sarcoid granulomas of the iris are homogenous epithelioid cell aggregates. On the other hand, VKH is a multisystem autoimmune disorder principally affecting pigmented tissues in the ocular, auditory, integumentary, and central nervous systems. Inomata and Rao reported the histological changes that occur during the different stages of VKH include a granulomatous process in the acute and chronic recurrent phase, and non-granuomatous inflammation during the convalescent phase[21)]. Uveal granulomatous inflammations are usually divided into three distinct morphologic categories: zonal, sarcoidal, and diffuse[22)]. Sarcoid granulomatous inflammation consists of a discrete, well-delineated collection of epithelioid cells surrounded by lymphocytes. This granulomatous process is typically devoid of necrosis, and multinucleated giant cells can be observed at the site of epithelioid cell collections. In contrast, diffuse granulomatous inflammation is indicative of lymphocytic infiltration throughout the uvea interrupted by focal collection of epithelioid hisiocytes with or without multinucleated giant cells. VKH is a typical example of diffuse granulomatous uveitis. We postulate that the different inflammation mechanism underlying sarcoidosis and VKH might have affected our results.

Iris nodules are an important diagnostic clue in the evaluation of uveitis. Although sarcoidosis and VKH are the common granulomatous uveitides in Japan, onset time, regions of development, duration and therapeutic response of iris nodules differ. Prospective trials are necessary to address more accurately the clinical features and therapeutics of uveitis with iris nodules.

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ぶどう膜炎に伴う虹彩結節—サルコイドーシスと Vogt-小柳-原田病の比較

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〔目的〕ぶどう膜炎でみられる虹彩結節の臨床像を，その出現頻度が高いサルコイドーシスと Vogt-小柳-原田病（VKH）について比較検討した．〔対象および方法〕2003 年 7 月～2004 年 10 月に当科を受診した，連続したぶどう膜炎患者 547 名の診療記録をレトロスペクティブに調べた．サルコイドーシス確定診断群（S 群）の 109 例 205 眼（平均 57.6±16.2 歳），VKH 確定診断群（V 群）の 21 例 42 眼（平均 58.8±15.3 歳）にみられた虹彩結節の頻度，出現時期，部位，観察された期間および治療法を比較した．〔結果〕全ぶどう膜炎患者 547 例中 50 例（9.1%）に虹彩結節を認めた．虹彩結節は S 群の 37 眼（18.0%），V 群の 13 眼（31.0%）にみられ，出現頻度に有意差はなかった．結節の出現時期および部位は，S 群は 26 眼（70.3%）の虹彩または隅角結節が初発時にみられ，V 群は 13 眼すべて Koeppe 結節が再発時にみられ，統計学的に有意差を認めた（$p<0.00002$）．虹彩結節の観察された期間は，S 群 2.1±0.2 週，V 群 5.0±1.0 週で，V 群は S 群より有意に長かった（$p<0.02$）．V 群におけるステロイド治療により虹彩結節が消退するまでの期間は，局所点眼群 9.6±1.4 週，内服群 5.8±2.0 週，テノン氏嚢内注射 2.6±0.6 週で，テノン氏嚢内注射が早期に結節を消退させた．〔結論〕サルコイドーシスと VKH は，肉芽腫性虹彩結節を生じる代表的な疾患である．両疾患における虹彩結節の出現頻度には差がなかったが，出現時期および部位，持続期間，治療への反応は異なり，虹彩結節の病態が異なる可能性が示唆された．