


Tackling HTLV-1 infection in ophthalmology: a nationwide survey of ophthalmic care in an endemic country, Japan

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Received 5 December 2019

Revised 5 February 2020

Accepted 20 February 2020



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To cite: Kamoi K, Okayama A, Izumo S, *et al.* *Br J Ophthalmol* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bjophthalmol-2019-315675

ABSTRACT

Introduction Japan is the most endemic of the developed nations in terms of human T-lymphotropic virus type 1 (HTLV-1) infection. Japan has been tackling HTLV-1 infection and has made remarkable progress. In ophthalmology, awareness of the association between HTLV-1 infection and uveitis has been increasing since the 1990s, when the relationship was first established. Here, we describe a nationwide survey and analysis of the current state of medical care for HTLV-1-associated uveitis (HAU) at ophthalmic facilities in Japan.

Methods A questionnaire survey covered all university hospitals in Japan that were members of the Japanese Ophthalmological Society and all regional core facilities that were members of the Japanese Ocular Inflammation Society. Survey data were collected, and nationwide data on the state of medical care for HAU were tallied and analysed.

Results Of the 115 facilities, 69 (60.0%) responded. HAU was most commonly diagnosed 'based on blood tests and characteristic ophthalmic findings'. Overall, 86.8% of facilities perform testing for HTLV-1 antibodies during medical care for diagnosing uveitis, with 58.3% routinely performing testing. Facilities with experience in providing medical care for HAU accounted for 67.6%. The survey also revealed that 85.5% of facilities had seen no decrease in the number of patients with HAU.

Conclusions In the two decades since the establishment of HAU as a pathological entity, the majority of facilities in Japan have started performing testing for HTLV-1 antibodies when considering differential diagnoses for uveitis. Our data suggest that providing information on HTLV-1 infection to ophthalmologists in Japan has been successfully implemented.

INTRODUCTION

Human T-lymphotropic virus type 1 (HTLV-1) is the first retrovirus known to infect humans and cause disease.¹⁻³ Globally, HTLV-1 has gained increasing attention since it was discovered that more than 40% of Aboriginal individuals in central Australia are infected with HTLV-1.⁴ Several papers regarding the importance of this virus have been published and have gained the attention of global health agencies such as the WHO and individuals involved in healthcare.^{5,6}

Among advanced nations, Japan is believed to have the highest number of HTLV-1 infections, at approximately 1.08 million individuals.⁷ Japan has

been taking a leading role in fundamental research and clinical research regarding HTLV-1,⁶ resulting in major contributions to the establishment of various pathological entities as HTLV-1-associated diseases.

HTLV-1 has been revealed to cause diseases such as adult T-cell leukaemia/lymphoma (ATL),^{2,3} HTLV-1-associated myelopathy (HAM)^{8,9} and HTLV-1-associated uveitis (HAU).¹⁰⁻¹⁴ HAU requires ophthalmic care, and is currently the most common form of uveitis in high-prevalence regions.¹⁵ Although intensive ophthalmic care had been performed in endemic areas such as Kyushu, the increased mobility of populations in modern society has resulted in HTLV-1 carriers being identified throughout Japan, with particularly prominent increases reported in urban areas.¹⁶

In the 1990s, the first set of evidence for HTLV-1 as a cause of uveitis was reported with clinical and laboratory data. Since then, uveitis has been well established as significantly related to HTLV-1.^{17,18} Japanese ophthalmologists have been providing the latest information on care for HAU in many ways, including presentations in conferences and the publication of papers.

Although two decades have passed since the establishment of HAU, the present state of medical care for HTLV-1 in the ophthalmic field throughout Japan remains unknown. Moreover, the current concerns of ophthalmologists in treating HTLV-1-infected patients remain unclear. For example, although immunosuppressants and biologicals have been used in recent years to treat uveitis,¹⁹ and have produced dramatic results, information is lacking on the pros and cons of using such medications for HTLV-1-infected individuals.²⁰

As such, this study is the first investigation aimed at shedding light on the current state of medical care for HAU in Japan through a nationwide survey. We believe that information on the current status of ophthalmic approaches in Japan will be of great use for other, newly revealed HTLV-1 endemic areas, as well as other departments treating HTLV-1 infections.

METHODS

In March 2015, a questionnaire survey regarding the state of medical care for HAU was sent to a total of 115 facilities, including all university hospitals, throughout Japan that were members of the Japanese Ophthalmological Society and all ophthalmic



Figure 1 A map showing the regions of Japan. The Kanto and Kinki regions are metropolitan areas in Japan with population growth due to population movement in recent years, and the Kyushu region has a high prevalence of human T-lymphotropic virus type 1 (HTLV-1). Source: Wikimedia Commons (https://commons.wikimedia.org/wiki/File:Regions_and_Prefectures_of_Japan_2.svg).

facilities providing medical care for ocular inflammation that were members of the Japanese Ocular Inflammation Society.

The questionnaire survey was conducted by mail beginning in January 2015 and lasting until March 2015. Questions were created by discussion among the group of HTLV-1 experts belonging to the teams from the Ministry of Health, Labour and Welfare research group of Japan and the Japan Agency for Medical Research and Development.

Questions focused on facility location and classification, methods for diagnosing ocular manifestations of HAU, experience with ophthalmic care for HAU, testing for HTLV-1 antibodies in considering differential diagnoses for uveitis, timing of testing for HTLV-1 antibodies, measurement of HTLV-1 antibodies when using immunosuppressants or biologicals and provision of information in the future regarding HTLV-1 infection in the field of ophthalmology (figure 1, table 1).

Only valid responses to questions were included in the statistical analyses. If a respondent left a question blank, only that blank response was excluded from analysis. Data on categories pertaining to medical care for HAU were tallied and analysed.

RESULTS

Of the 115 facilities, 69 responded (response rate, 60.0%). Facilities throughout Japan responded, with those in the Kanto region accounting for 39.1% of overall respondents and those in the high-prevalence Kyushu region accounting for 13.0%. By type of

Table 1 Questionnaire used to assess the state of medical care for HAU

(1) How do you diagnose HAU?	Based on a blood test (positive for HTLV-1 antibodies) and the characteristic ophthalmic findings Based on a test of intraocular fluid (PCR test) and the characteristic ophthalmic findings Other (please provide the specifics):
(2) Do you exclude other forms of uveitis when diagnosing HAU?	Yes No Other ()
(3) Has your department ever provided ophthalmic care for patients with HAU?	Yes No
(4) Is the number of new patients with HAU rising or declining?	Rising No change Declining
(5) Do you test for HTLV-1 antibodies in considering differential diagnoses for uveitis?	Yes No/unidentified
(6) What is the timing of testing for HTLV-1 antibodies?	Carried out routinely in considering differential diagnoses for uveitis When ocular manifestation such as HAU, ATL or HAM is suspected When requested by patient When administering steroid When administering immunosuppressant When administering biological product When performing surgery Others
(7) Are HTLV-1 antibodies measured when using an immunosuppressant or biological?	Yes (all cases) Yes (selected cases) No
(8) Do you think measurement of HTLV-1 antibodies was preferable when using an immunosuppressant or biological?	Yes No Don't know
(9) Is provision of information regarding HTLV-1 infection necessary?	Yes (please provide the specifics): No

ATL, adult T-cell leukaemia/lymphoma; HAM, HTLV-1-associated myelopathy; HAU, HTLV-1-associated uveitis; HTLV-1, human T-lymphotropic virus type 1.

facility, 55.0% of overall respondents were advanced treatment hospitals, 42.0% were hospitals and 2.9% were clinics.

The survey showed that HAU was most commonly diagnosed ‘based on blood tests and characteristic ophthalmic findings’ in 98.4% of facilities, and ‘based on a test of intraocular fluid and characteristic ophthalmic findings’ in 6.5% of facilities (table 2). Regarding whether differential diagnosis was practised by excluding other forms of uveitis when diagnosing HAU, 96.8% responded ‘Yes’.

Regarding the provision of ophthalmic care for HAU, 67.6% of facilities indicated that they had experience in providing such care (table 3). In terms of whether the number of new patients with HAU was rising or declining, the answer was ‘unchanged’ for 85.5% of respondents, ‘in decline’ for 12.7% and ‘on the rise’ for 1.8%.

When considering differential diagnoses for uveitis, overall, 86.8% of facilities performed testing for HTLV-1 antibodies, while 13.2% did not. By region, 100% of facilities in the Kyushu and Shikoku/Chugoku regions performed HTLV-1 antibody testing. However, metropolitan areas such as Chubu and Kinki showed frequencies that were not particularly high, at 77.8% and 66.7%, respectively (table 4). As for the timing of HTLV-1 antibody testing, 58.3% of facilities performed routine testing when providing medical care for uveitis, and 41.7% performed testing on suspicion of an HTLV-1-related ocular manifestation (table 5).

Table 2 Diagnostic procedure for HAU

Diagnostic methods	Northern (n=5)	Central/metropolitan (n=41)			Southern (n=16)		Total
	Hokkaido/Tohoku (n=5)	Kanto (n=22)	Chubu (n=8)	Kinki (n=11)	Chugoku/Shikoku (n=7)	Kyushu (n=9)	
Blood test and ophthalmic examination	100.0%	97.6%			100.0%		98.4%
	100.0%	100.0%	87.5%	100.0%	100.0%	100.0%	
Intraocular fluid test and ophthalmic examination	20.0%	11.1%			6.3%		6.5%
	20.0%	4.5%	0.0%	9.0%	0.0%	11.1%	
Others	0.0%	19.4%			0.0%		3.2%
	0.0%	0.0%	12.5%	0.0%	0.0%	0.0%	

HAU, HTLV-1-associated uveitis.

Regarding the question of whether HTLV-1 antibodies were measured when using an immunosuppressant or biological, 28.8% of facilities indicated that, in principle, such measurement was performed, 21.2% indicated that measurement was performed for selected cases and 50.0% indicated that, in principle, measurement was not performed. When asked whether measurement of HTLV-1 antibodies was preferable when using an immunosuppressant or biological, 38.8% answered 'Yes', 6.0% answered 'No' and 55.2% answered 'Don't know'.

Regarding provision of information in the future, 72.3% of facilities indicated that this was necessary, and 27.7% indicated that there was no particular need. The following items of information were considered necessary by two or more respondents: results of up-to-date epidemiological surveys; routes of infection; treatments and prognoses; risks associated with immunosuppressants and biologicals; and details of informed consent (data not shown).

DISCUSSION

Among the advanced nations, Japan has the highest number of HTLV-1-infected individuals,⁷ making accurate information on HTLV-1-infected individuals readily available.¹⁸ Since HAU was established as a distinct pathological entity,^{17,18} new information on HAU has been continuously shared among ophthalmologists in Japan. In particular, ophthalmologists in the endemic southern areas of Japan such as Kyushu have been keen to clarify the role of this retrovirus in the differential diagnoses of uveitis (tables 2–5). In fact, HAU is still the most commonly encountered clinical form of uveitis in southern Kyushu.²¹ With population movement becoming more frequent, the number of HTLV-1-infected individuals has been growing in low-prevalence regions.^{22,23} As a result, attention to this retrovirus is currently warranted, particularly in urban areas.¹⁶ This survey in the ophthalmic field is highly significant in terms of the reflection of both two decades of educational effort in the field of ophthalmology in Japan and the spread of HTLV-1 infection (tables 2–5).

In Japan, differential diagnosis was practised extensively when diagnosing HAU in almost all facilities that responded, showing

that definitive diagnosis of HAU is highly reliable, by excluding other forms of uveitis when diagnosing HAU (table 4). This might be a reflection of the effect of continuous educational efforts on ophthalmologists in Japan. As such, the survey showed that nearly 70% of facilities have experience in providing medical care to patients with HAU, and that facilities with experience are located throughout Japan (table 3). This shows that patients are seen in the Kyushu region, which has been a high-prevalence region, and that there is a trend towards these patients dispersing throughout Japan, particularly to urban areas such as in the Kinki and Kanto regions. This is associated with the influx of people into urban areas, and this result corroborates previous reports.^{16,23}

This survey found no decline in the number of new patients with HAU in nearly 90% of facilities. In Japan, HTLV-1 antibody screening of all donated blood in the country has been conducted by the Japanese Red Cross since 1986. The widespread implementation of infection control measures has almost eliminated infection thanks to breast milk or blood transfusion serological screening tests for HTLV-1 in blood donors, as started in 1987 in Nagasaki, an endemic area of Japan.^{6,24} Routine HTLV-1 antibody testing has been added to antenatal pregnancy screening throughout Japan since 2010. These measures against HTLV-1 have basically eliminated infusion-related and mother-to-child infections. However, the number of HTLV-1-infected patients has not decreased significantly and around 1.08 million HTLV-1-infected patients still exist in Japan. According to a recent analysis of the Japanese Red Cross Blood Centers' database, the number of newly HTLV-1-infected individuals was highest among women aged 50–59 years and men aged 60–69 years in both endemic and non-endemic areas.²³ This suggests that carriers infected before implementation of the infection control measures or carriers exposed to horizontal infection through routes such as sexual contact are now developing HAU and no decreasing trend in new patients with HAU has yet been seen. HAU clearly still warrants attention.

This survey also showed that, in Japan, more than half of facilities measure HTLV-1 antibodies when diagnosing uveitis, and

Table 3 Experience in providing medical care to patients with HAU

Experience of medical care for patients with HAU	Northern (n=5)	Central/metropolitan (n=46)			Southern (n=16)		Total
	Hokkaido/Tohoku (n=5)	Kanto (n=26)	Chubu (n=8)	Kinki (n=12)	Chugoku/Shikoku (n=7)	Kyushu (n=9)	
Yes	100.0%	58.7%			92.3%		67.6%
	100.0%	53.8%	62.5%	66.7%	100.0%	88.9%	
No/unidentified	0.0%	42.3%			7.7%		32.4%
	0.0%	46.2%	37.5%	33.3%	0.0%	11.1%	

HAU, HTLV-1-associated uveitis.

Table 4 Test for HTLV-1 antibodies in considering differential diagnoses for uveitis

Test for HTLV-1 antibodies in considering differential diagnoses for uveitis	Northern (n=5)	Central/metropolitan (n=47)			Southern (n=16)		Total
	Hokkaido/Tohoku (n=5)	Kanto (n=26)	Chubu (n=9)	Kinki (n=12)	Chugoku/Shikoku (n=7)	Kyushu (n=9)	
Yes	80.0%	82.9%			100.0%		86.8%
	80.0%	80.1%	77.8%	66.7%	100.0%	100.0%	
No/unidentified	20.0%	17.1%			0.0%		13.2%
	20.0%	19.9%	22.2%	33.3%	0.0%	0.0%	

HTLV-1, human T-lymphotropic virus type 1.

that if facilities that perform such measurement when an HTLV-1-related ocular manifestation is suspected are also counted, nearly 90% of facilities measure HTLV-1 antibodies (table 4). This high percentage is unique to Japan among the nations of the world, due to the high prevalence of HTLV-1 infection and high awareness of HTLV-1 among ophthalmologists. This has also helped identify HTLV-1-infected patients throughout Japan. Nonetheless, in areas of low prevalence, some facilities perform no measurement of HTLV-1 antibody titres when diagnosing uveitis, suggesting that some cases of HAU may remain undiagnosed. This represents a key obstacle to overcome in Japan, even after two decades of educational trials.

Given past reports of patients developing ATL while undergoing treatment with an immunosuppressant (tacrolimus) after organ transplant, whether treatment of HTLV-1-infected individuals with an immunosuppressant or biological is beneficial remains contentious. For instance, reports have described reactivation of hepatitis B during treatment with a biological product (anti-tumour necrosis factor- α antibody) in hepatitis B carriers,²⁵ and caution is now known to be warranted when prescribing a biological to a hepatitis B carrier. One case has already been reported in which a patient with rheumatoid arthritis and HTLV-1 infection experienced exacerbation of HTLV-1-associated conditions such as myopathy and uveitis after using a biological agent (tocilizumab).²¹ To date, no set conventions have been determined for prescribing immunosuppressants or biologicals to HTLV-1 carriers. In recent years, such medications

have been prescribed to treat Behçet disease and other forms of non-infectious uveitis.²⁶ However, no measurement of HTLV-1 antibodies is performed in 50.0% of facilities prescribing such treatment in this survey. A majority of such facilities stated that the reason for this was a lack of knowledge regarding whether it is better to perform the measurement. Although we have reported the safety of infliximab, the first biological agent applied to inflammatory diseases, for the eye under HTLV-1 infectious conditions *in vitro*,²⁰ further investigation of the justification for using immunosuppressants or biologicals in HTLV-1 carriers requires detailed surveys and assessments of whether administration of such medications activates HTLV-1 and whether such medications have any effect on the human body. The present survey also showed that knowledge on HTLV-1 when providing medical care for HAU has not been shared extensively. More than 70% of facilities indicated that provision of information is necessary regarding HTLV-1 infection and ophthalmic care. This is attributable to the dearth of information available on HAU and other HTLV-1-related ocular manifestations. From now on, active provision of information on ocular manifestations will be important.

Several potential limitations to this study need to be considered. First, although we were able to obtain responses from 60% of institutions, those facilities without experience in treating HAU may well have been more likely to not submit a response. Second, some degree of selection bias was likely present in this study. As patients with marked uveitis tend to be referred to

Table 5 Timing of testing for HTLV-1 antibodies

Timing of testing for HTLV-1 antibodies	Northern (n=4)	Central/metropolitan (n=40)			Southern (n=16)		Total
	Hokkaido/Tohoku (n=4)	Kanto (n=22)	Chubu (n=7)	Kinki (n=11)	Chugoku/Shikoku (n=7)	Kyushu (n=9)	
Carried out routinely in considering differential diagnoses for uveitis	50.0%	52.5%			84.6%		58.3%
	50.0%	50.0%	57.1%	54.5%	75.0%	88.9%	
When ocular manifestation such as HAU, ATL or HAM is suspected	50.0%	47.5%			25.0%		41.7%
	50.0%	50.0%	42.9%	45.5%	42.9%	11.1%	
When requested by patient	0.0%	7.5%			0.0%		5.0%
	0.0%	4.5%	0.0%	18.2%	0.0%	0.0%	
When administering steroid	25.0%	2.5%			0.0%		3.3%
	25.0%	0.0%	0.0%	9.1%	0.0%	0.0%	
When administering immunosuppressant	25.0%	2.5%			0.0%		3.3%
	25.0%	0.0%	0.0%	9.1%	0.0%	0.0%	
When administering biological product	20.0%	0.0%			0.0%		1.7%
	20.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
When performing surgery	0.0%	5.0%			0.0%		3.3%
	0.0%	0.0%	14.3%	9.1%	0.0%	0.0%	
Others	0.0%	10.00%			0.0%		6.7%
	0.0%	18.2%	0.0%	0.0%	0.0%	0.0%	

ATL, adult T-cell leukaemia/lymphoma; HAM, HTLV-1-associated myelopathy; HAU, HTLV-1-associated uveitis; HTLV-1, human T-lymphotropic virus type 1.

main facilities in Japan, responses to this survey were obtained from main facilities such as university hospitals and regional core facilities. This survey therefore might not cover the actual state of medical care among small clinics that would be the source of referrals in many cases. Third, the survey was not set up to require mandatory responses to questions, so the number of answers collected differed according to the contents of the question. This might have influenced data analysis and interpretation. Fourth, this survey did not ask for details of enrolled patients such as clinical features and therapeutic methods. This choice was made to avoid placing excessive burdens on respondents and their institutions, in an effort to maximise the response rate. However, this missing information would clearly be of interest to ophthalmologists, and we plan to obtain more detailed information on clinical features and treatments in future surveys using a questionnaire with a more streamlined design.

In conclusion, this survey showed that the majority of ophthalmic facilities in Japan examine HTLV-1 infection when diagnosing uveitis, although no international guidelines of ophthalmology have recommended the measurement of HTLV-1 antibody when diagnosing uveitis. This achievement reflects the effects of two decades of educational efforts regarding HAU among ophthalmologists in Japan, and the effect was considerably widespread throughout Japan. With the increasing mobility of the population, the number of such individuals is on the rise even in regions that have historically shown a low prevalence, representing another emerging problem to solve in Japan. Much more education is necessary in previous non-endemic regions. The present survey identified the current status of medical care for HTLV-1 in ophthalmology in an endemic advanced nation. This nationwide survey on HAU provided an example of valuable information for the medical care of patients with HTLV-1-related diseases. This information could serve as a good model for other countries tackling HTLV-1 infection.

Acknowledgements We thank the ophthalmologists in the responding facilities for their assistance with data collection.

Contributors KK designed the study and wrote the draft of the manuscript. AO designed the study. SI, IH, KU, AT, TW and KOM contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All authors critically reviewed and approved the final manuscript.

Funding This study was supported by grants from the Research Program on Emerging and Re-emerging Infectious Diseases from the Japan Agency for Medical Research and Development (AMED) (ID: 15652551, 15652670, JP18fk0108037), and Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan (ID: 14427084).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This cross-sectional study was performed in Japan after obtaining ethics approval from both Tokyo Medical and Dental University and the Institute of Medical Science at the University of Tokyo, in accordance with the tenets of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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