10:40 - 11:55

Session Ⅱ　トピックス

座長：高橋　啓（東邦大学医療センター大橋病院病理）

平橋淳一（東京大学医学部附属病院腎臓内分泌内科）

3-1 心筋炎における細胞外基質関連蛋白の発現とその影響についての検討

塙　晴雄[1]、林　学[1]、吉田　剛[1]、羽尾和久[1]、丁　立民[1]、吉田香織[1]、小玉　誠[1]、
太田好美[2]、相澤義房[1]

[1)]新潟大学大学院医歯学総合研究科　循環器学分野

[2)]新潟大学医学部保健学科

3-2 リューコキャッチを用いた慢性糸球体腎炎診断法の開発

野島　博

大阪大学微生物病研究所・分子遺伝研究分野（感染症ＤＮＡチップ開発センター）

3-3 IL-25 と慢性炎症

中島裕史（千葉大学大学院医学研究院　遺伝子制御学 医学部附属病院　アレルギー・膠原病内科）

3-4 MPO-ANCA 産生感受性遺伝子 Man-1 の本体解明－6,000 genotyping 追加による進展－

濱野慶朋[1]　長尾朋和[2]　吉澤寛道[1]　草野英二[1]　鈴木和男[2]　湯村和子[1]

[1]自治医科大学　腎臓内科　[2]千葉大学大学院医学研究院　免疫発生学

3-5 MPO-KO マウスおよび CGD マウスのカンジダ死菌による肺炎の誘発

荒谷康昭、三浦典子*、大野尚仁*

横浜市立大学大学院生命ナノシステム科学研究科

*東京薬科大学薬学部

12:00 - 12:30

Closing Remarks

橋本博史（順天堂大学）

直江史郎（桐蔭横浜大学）

岡崎富男（呉共済病院）

研究成果の刊行に関する一覧表

雑誌					
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研究成果の刊行に関する一覧表

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山縣邦弘	急速進行性糸球体腎炎	今井圓裕	腎臓内科レジデントマニュアル	診断と治療社	東京	2010年	
今井圓裕	ネフローゼ症候群診療指針ダイジェスト版	今井圓裕	ネフローゼ症候群診療指針ダイジェスト版	東京医学社	東京	2011年	
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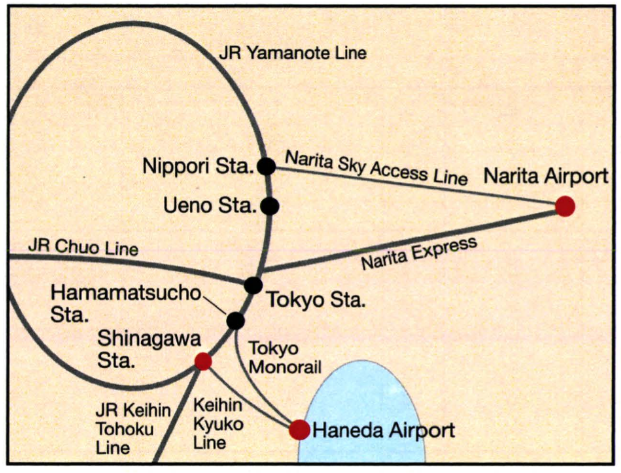

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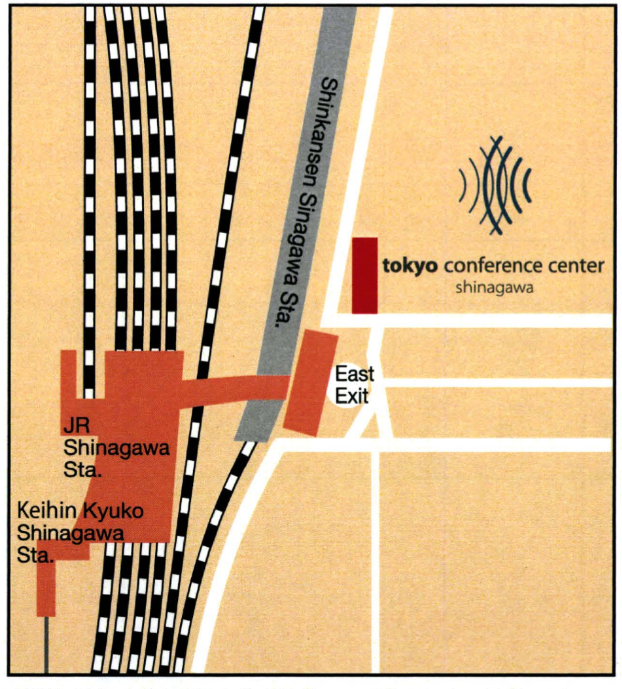

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The Asia Pacific Meeting of Vasculitis and ANCA Workshop 2012

Date: March 28 (Wed) - 31(Sat), 2012
Venue: Shinagawa, Tokyo, Japan
tokyo conference center shinagawa

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shinagawa

International Faculty Members

Asian-Pacific

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Australia : Judith Anne Savige (Melborne)
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The Asia Pacific Meeting of Vasculitis and ANCA Workshop 2012

Program

	28 (Wed)	29 (Thu)	30 (Fri)	31 (Sat)
8:00-9:00		Master Lecture 2	Master Lecture 3	Master Lecture 4
9:00-12:00		Symposium 2	Symposium 4	Symposium 6
12:00-13:00	Registration	Luncheon Seminar 1 Luncheon Seminar 2	Luncheon Seminar 3 Luncheon Seminar 4	Luncheon Seminar 5 Luncheon Seminar 6
13:00-15:00	Opening Remarks Welcome Lecture (Kazuo Suzuki) Master Lecture 1	Symposium 3	Symposium 5	Plenary Lecture 2 Closing Remarks (Shoichi Ozaki, Hirofumi Makino)
15:00-18:00	Coffee Break Symposium 1	Coffee Break Poster Session 1 Poster Workshop 1	Coffee Break Poster Session 2 Poster Workshop 2	
18:00-19:00	Plenary Lecture 1	Special Lecture 1	Special Lecture 2 (Tomisaku Kawasaki)	
19:00-	Reception	Mixer	Banquet	

Topics

Special Lecture
-Kawasaki disease
-Takayasu arteritis

Plenary Lecture
-Classification and diagnosis of vasculitis syndrome
-New generation therapy of ANCA-associated vasculitis

Luncheon Seminar
-IVIG in Kawasaki disease
-IVIG in Churg-Strauss syndrome
-Anti-TNF therapy
-Rituximab
-Anti-IL-6 receptor antibody
-Mizoribine
-FK506
-Plasmapheresis

Master Lecture
-Genetics in ANCA-associated vasculitis
-Renal involvement in ANCA-associated vasculitis
-Pulmonary involvement in ANCA-associated vasculitis
-Skin and neuronal involvement in ANCA-associated vasculitis

Symposium
-Kawasaki disease
-Large vessel vasculitis in Asia and Western countries
-Medium to small vessel vasculitis in Asia and Western countries
-Clinical trials of MPO-ANCA-associated vasculitis
-Therapeutic angiogenesis
-Pathogenesis of vasculitis syndrome

Review

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Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis, Large Vessel Vasculitis and Kawasaki Disease in Japan

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Key Words

Myeloperoxidase · Anti-neutrophil cytoplasmic antibody · Vasculitis · Epitope analysis · Rapidly progressive glomerulonephritis · Microscopic polyangiitis · Kawasaki disease · Systemic vasculitis · Epitopes

Abstract

Based on studies comparing the prevalence of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) between Japan and Europe, we have learned that the difference may be due to genetic background and environmental factors, but not to diagnosis or ELISA system for myeloperoxidase and proteinase-3 ANCA. In Japan, microscopic polyangiitis is the most common among AAV, but Wegener's granulomatosis was present in less than 2 per million patients. Also, one study from Hokkaido reported only 16 patients in a 27-year time frame. A recent retrospective study of renal vasculitis between 2000 and 2004 from Miyazaki prefecture in Japan reported an incidence of microscopic polyangiitis of 14.8 per million, but no patients with Wegener's granulomatosis or Churg-Strauss syndrome. In the present review, we focus on ANCA-related vasculitis in Japan: (1) AAV and large vessel vasculitis – Takayasu's arteritis and giant cell arteritis; (2) primary renal vasculitis; (3) epitopes of myeloperoxidase-ANCA in vasculitis in the Japanese population and comparison of ANCA-ELISA systems in Japan and Europe, and finally (4) children with vasculitis in Japan involving Kawasaki disease – a systemic vasculitis.

Introduction

In the late 1990s, discussions suggested more widespread variations in disease frequency, with Wegener's granulomatosis (WG) being rare in Japan, where proteinase-3 (PR3) anti-neutrophil cytoplasmic antibody (ANCA) antibodies were rarely detected. The majority of patients with renal vasculitis have myeloperoxidase (MPO) antibodies and are classified as having microscopic polyangiitis (MPA). Furthermore, prevalence studies from Japan have estimated that WG is present in less than 2 per million patients, suggesting an incidence of less than 0.1 million per year, according to the Research Group of Epidemiology and Intractable Diseases, supported by a grant of The Ministry of Health, Labour and Welfare, Japan [1, 2].

The hypothesis that the different genetic and environmental background between Japan and Europe would lead to a difference in the clinical phenotype has been investigated. One of the original hypotheses that the distri-

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bution of vasculitis phenotypes and ANCA specificities would vary with latitude has not been confirmed or refuted [3]. Japan is located between the latitude 26° to 45° North [4]. There exist interesting concordance and discordance of clinical features of vasculitis between Japan and Europe/USA. The differences will be reviewed here.

Vasculitis is much more heterogeneous in its clinical features such as incidence, phenotype and/or genotype among areas. As few giant cell arteritis (GCA) patients have been reported in Japan, compared with Europe and the USA [5], the prevalence of GCA in studies in Japan will be also reviewed and discussed. Moreover, differences in renal involvement in WG and MPA between the UK and Japan [6] will also be discussed. These area differences will be reviewed in association with human leukocyte antigen (HLA) such as cANCA-positive WG in 1996 [7], and autoreactive T cell response MPO fragments [8, 9].

A good correlation between the extent of crescent formation and the MPO-ANCA titer has been demonstrated [10]. Differences in reactivity suggest differences of binding to MPO epitopes by MPO-ANCA. The titer of MPO-ANCA does not always reflect disease activity, and this inconsistency may be attributable to differences in epitopic specificity by MPO-ANCA between patients. We also review the analyses of the epitopes in MPO-ANCA in the Japanese population. Epitopes on MPO recognized by MPO-ANCA from patients with MPO-ANCA-associated vasculitis in the Japanese population have been analyzed using recombinant MPO fragments [11]. Differences in binding specificity may influence the pathogenic potential of the antibodies. The immunodominant epitopes have not been precisely defined. Erdbrügger et al. [12] reported that PR3-ANCA and MPO-ANCA do not interfere with the enzymatic activity of MPO. The differences in binding specificity may influence the pathogenic potential of the antibodies [13]. Van der Geld et al. [14] demonstrated that noncontiguous amino acids are important to the structure of epitopes. In this review, the epitopes in patients with vasculitis in Japan will be discussed. Concomitantly, ELISA systems for three kinds of MPO-ANCA and PR3-ANCA used in Japan have been compared with those commonly used in Europe. The report of Ito-Ihara et al. [15] that described ANCA ELISA systems in Japan will mainly be reviewed.

Finally, we will review Kawasaki disease (KD), a systemic vasculitis in childhood prevailing in Japan that was first described in 1967 by Dr. Tomisaku Kawasaki. The nationwide surveys for KD conducted every 2 years show that the number of KD patients has been increasing [16]. KD is now appearing all over the world, but is most prevalent in Japan and Asian countries [16, 17].

Thus, in this review, we describe ANCA-associated vasculitis (AAV) and other vasculitis including large vessel vasculitis (Takayasu's arteritis, TAK) and GCA and KD in Japan. Epitopes of MPO-ANCA in vasculitis in the Japanese population and a comparison of ANCA-ELISA systems in Japan and Europe are also described.

Vasculitides in Japan and Europe/USA

Differences in the Clinical Presentation of Vasculitis between Japan and Other Countries

It is important to study and understand the concordance and discordance of clinical features of vasculitis between populations in Japan and Europe and the USA. Compared to rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), vasculitis is much more heterogeneous in its clinical features, such as incidence, phenotype and/or genotype among areas and/or countries.

TAK and GCA are two types of vasculitis where inflammation occurs in the large vessels, and their granulomatous vasculitis with the presence of giant cells [18, 19]. Compared with Europe and the USA, fewer GCA patients and a higher incidence of TAK patients are reported in Japan. The point prevalence of GCA in studies from Japan in 1997 was 690 patients (95% CI 400–980) [5]. The prevalence of patients aged more than 50 years was 1.48/million compared with 200 in the USA and 60 in Spain [20, 21].

We have been asking ourselves why there are so few GCA patients in Japan. One factor leading to this question is the fact that we do not frequently see patients with ankylosing spondylitis in Japan, which is not the case in Korea and China. The incidence of HLA-B27 in Japan is only 0.3% compared with about 5% in Korea and China and 7–14% in the USA and Europe [22]. Therefore, genetic factors affecting the incidence of the disease must be unique even among far eastern countries. HLA-DRB1*0401 or HLA-DRB1*0404 are predominantly (60%) detected in patients with GCA in the USA; however, HLA-DRB1*0401 and HLA-DRB1*0404 are less frequent, 2.9 and 0.7%, respectively, as determined in 493 Japanese healthy individuals compared with 15.9 and 3.2%, respectively, in 60 healthy individuals in the USA [19]. This is one of the reasons why the incidence and/or prevalence of GCA is not high in Japan.

In Japan, TAK is predominant in young female patients and mainly affects the aortic arch (type I), as determined

Table 1. Point prevalence of vasculitis patients in Japan

Year of investigation	Disease	Estimated number of patients	Average age of patients at the time of study, years	Male/female
1993	Takayasu's arteritis	4,800	35–65	1/10
1994	Polyarteritis nodosa	1,400	56.2	1/1.1
	Wegener's granulomatosis	670	46.2	1/1.2
	Allergic granulomatous angiitis (Churg-Strauss syndrome)	450	47.1	1/1.1
	Buerger's disease	10,000	45–65	9.7/1
	Malignant rheumatoid arthritis	4,200	53	1/2.2
1998	Giant cell arteritis (temporal arteritis)	690	62.9	1/1.6
	ANCA-associated vasculitis	2,700	59	1/1.8

by angiography. The patients show significantly high levels of HLA-B52 (56%) and HLA-B39 (17%) compared with healthy controls (25 and 6%, respectively) [23]. However, it was reported that a larger number of patients with TAK in India and other East Asian countries are middle-aged males with affected abdominal aortas (type III), and who have HLA-B39 [23]. A nationwide point prevalence survey in the form of a retrospective, hospital-based study was conducted in 1994 and 1998 (table 1). Although the data are not new and do not show the real incidence, the prevalence of vasculitis/vasculopathy in Japan understandable. Buerger's disease and TAK are common, but WG and GCA are not frequently observed in Japan.

In 1997, we conducted a retrospective, hospital-based, nationwide survey on Japanese patients with AVV. The survey reported 63 MPA, 28 WG and 12 Churg-Strauss syndrome (CSS) patients and 104 patients with undifferentiated AAV (most patients were renal-limited vasculitis of MPA analyzed by the records). The point prevalence of AVV in the 1997 survey demonstrated that MPA is the most common AVV in Japan. Among 207 AVV patients, PR3-cANCA and MPO-pANCA were demonstrated in 26.3 and 80.8%, respectively. Among 28 WG patients, PR3-cANCA and MPO-pANCA were shown in 86 and 14%, respectively; and among 63 patients with MPA in 22 and 87% of patients, respectively. For MPA, prominent manifestations were renal involvement (87.3%), mainly rapidly progressive glomerulonephritis (RPGN), and pulmonary involvement (63.5%) including interstitial pneumonia/pulmonary fibrosis (33.3%) and pulmonary hemorrhage (22.2%). Patients with MPA having only a pulmonary localized lesion have been reported. In addition, 93% of Japanese WG patients demonstrated the ear, nose and throat (ENT) features, whereas only 39% demonstrated renal involvement. Compared to WG patients in Europe and the USA, renal involvements are not common in Japanese WG patients. Furthermore, positive rate and titer of PR3-/cANCA are relatively low in WG patients who have localized ENT lesions. These results were included in the annual report for the Research Committee of Intractable Vasculitis, the Ministry of Health and Welfare, Japan, in 1998 by Hashimoto and colleagues.

The question why MPA is more common than WG in Japan while WG is the most common AVV in Europe and the US is important. This question led us to start an epidemiological study on Japanese patients with AVV in collaboration with the European Systemic Vasculitis Study Group (EUVAS) members Drs. D. Jayne, R. Watts, D. Scott, N. Rasmussen and U. Specks. The understanding of differences will lead to new insights into the etiology and pathogenesis of vasculitides.

Latitude of Japan

Japan is located between the latitude 26–45° North. Asahikawa city (43.5° North) on Hokkaido island is close to the latitude of Lugo, Spain (42°N). This is compatible with the latitude theory of AAV [4] (fig. 1).

Since we had to update old epidemiological data for AAV and determine the present incidence of AAV in Japan, we are glad to have started the new epidemiological study with UK/EUVAS members. Results of incidence of AAV in Miyazaki Prefecture are described in the section 'Primary Renal Vasculitis in Japan'.

It is interesting to note that a study from Beijing, China, demonstrated that 60.7% (54/89) of patients with WG were MPO-ANCA positive, 38.2% (34/89) were PR3-ANCA positive, and patients with MPO-ANCA had multisystem involvement and elevated initial serum creatinine level as compared with PR3-ANCA-positive WG patients [24, 25].

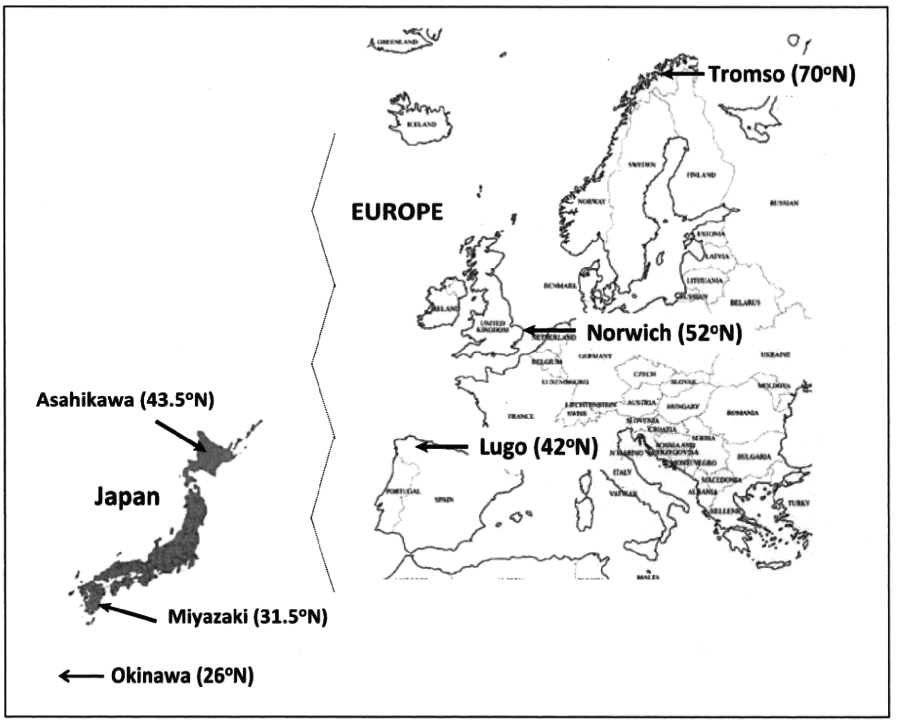

Fig. 1. Geographic difference in latitude between Japan and Europe.

Phenotype

The difference in the clinical presentation of TAK arteritis between Japan and countries in East Asia has been mentioned above; therefore, we will now discuss the differences in clinical presentation of patients with GCA between Japan and other countries. Our study demonstrates that no remarkable differences were found in the clinical features of patients with GCA between Japan and other countries, although GCA patients are not commonly found in Japan compared with the USA and Europe [19]. Further, differences in renal involvement in WG and MPA between the UK and Japan were demonstrated by Watts et al. [6]. The data that patients having a localized type of WG are more frequently found in Japan than WG patients with renal involvement were supported by Dr. Harabuchi at Asahikawa Medical University. A report from other ENT doctors with the same conclusion was published recently [26]. In fact, renal involvement was demonstrated in 12–40% of 21 WG patients in two reports. In another hospital-based, nationwide, retrospective study in Japan in 1988 and 1998, 39–63% of 172 patients had renal involvement. Renal involvement was found in 77% of 158 WG patients and 77% of 70 WG patients by Drs. Gross and Hoffman, respectively [27].

Genotype

A significant association of HLA-DRB1*0901 with MPA ($p = 0.037$, OR 2.44, 95% CI 1.33–4.46) as well as with MPO-ANCA positivity ($p = 0.014$, OR 2.44, 95% CI 1.41–4.22) was demonstrated by Tsuchiya and colleagues [28–31]. In their paper from 2003 [28], the Japanese diagnostic criteria for MPA proposed by the Research Committee on Intractable Vasculitides in 1998 were described. An interesting report regarding the association of HLA-DR9 in cANCA-positive WG (62.5%, 10/16 patients as compared with 26% of healthy controls; $p < 0.05$) was reported in 1996 [7]. The decreased activation potential of natural killer cells and/or T cells associated with killer cell immunoglobulin-like receptor/HLA genotypes was demonstrated in MPA patients, and insufficient resistance against infections in MPA patients was suggested [31]. Autoreactive T cell response to the MPO fragments was found, and several distinct epitopes on MPO fragments recognized by HLA-DR-restricted CD4+ T cells were demonstrated [8, 9].

Primary Renal Vasculitis in Japan

Experience of Vasculitis in Japan

We sometimes come across cases with MPA involving the kidney, most of which are MPO-ANCA positive.

Table 2. Difference in ANCA phenotype in patients with crescentic glomerulonephritis/microscopic polyangiitis/renal limited vasculitis between Japan and other countries

Country	Patients	Positive MPO-ANCA, %	Positive PR3-ANCA, %
USA [34]	107	64	36
EU [35]	80	63	25
Sweden [36]	99	48	32
UK [37]	153	65	25
Japan [38]	63	79	13
Japan [39]	369	90	8
Japan [40]	993	89	6

On the other hand, we rarely have the cases with PR3-ANCA-positive, crescentic glomerulonephritis and/or WG with renal involvement. However, in the European and American articles, much higher rates of the patients with positive PR3-ANCA and/or WG are shown among those with RPGN or AAV compared to Japan. In this section, we describe the epidemiology, the characteristics and outcome of ANCA-associated primary renal vasculitis (PRV): MPA, WG, and CSS with renal involvement, and renal limited vasculitis (RLV) in Japan comparing to those of European countries and the USA. Patients with PRV are defined according to the following criteria in accordance with EUVAS [32]: new patients with MPA, WG, CSS or RLV and renal involvement (elevated serum creatinine, hematuria, proteinuria, or red cell casts) attributed to active vasculitis with or without other organ involvement.

Epidemiology of PRV in Japan

In a nationwide, retrospective, hospital-based survey on RPGN recently conducted by the Japanese Society of Nephrology [33], the most frequent primary disease was RLV (42.1%), the second was MPA (19.4%) and the third was anti-glomerular basement membrane (anti-GBM) associated RPGN (6.1%). MPO-ANCA was positive in 88.1% of RLV patients and 91.8% of MPA patients. On the other hand, the prevalence of WG was only 2.6% among the total RPGN patients (n = 1,772), and the positive rate of PR3-ANCA among patients with RLV was 7.4%, that of MPA was 6.1%, and that of WG was 71.1%. These data were not different from previous studies in Japan. European and American studies revealed a third of RPGN/MPA/RLV patients were PR3-ANCA positive, which is clearly higher compared to Japan (table 2).

Until recently, the incidence, but not prevalence, of AAV has not been determined in Japan. We conducted the first population-based survey of PRV in Miyazaki Prefecture between 2000 and 2004 [2] based on recent epidemiological methods [41] and the sub-classification of AAV by the EUVAS [32]. Among 56 identified patients, 91% were MPO-ANCA positive and none had WG or CSS. The male/female ratio was 24/32, and the average age was 70.4 ± 10.9 (mean ± SD) years. The estimated annual incidence of PRV was 14.8 (95% CI 10.8–18.9) and 44.8 (95% CI 33.2–56.3) per million adults (over 15 years old) and seniors (over 65 years old), respectively. This value was reported to be 12.4 in Bristol, UK [42], 18 (95% CI 13–24) in Norfolk, UK [41], and 16 (95% CI 12–31) in Orebro, Sweden [36]. Thus, the annual incidence of PRV seems to be similar in Japan and Europe.

The race and genetic background of the patients should be closely related to the differences in rates of MPO-ANCA versus PR3-ANCA between Japan and Europe [28]. A geographic difference in the incidence of systemic vasculitides has also been suggested. The incidence of WG and MPA might be latitudinal; WG is frequently seen in high-latitude areas such as Sweden and the UK, while MPA in low-latitude areas such as Bahrain and Miyazaki. On the other hand, examination of the type of ANCA in sera from patients with AAV revealed that the results of commercially available ELISA kits used in EUVAS and Japan did not differ [15].

Clinical Phenotype and Features

Watts et al. [6], collaborators of Japan-UK vasculitis epidemiology study, have recently compared the incidence of PRV in the UK with Japan during the period 2000–2004 using the same case definitions. As shown in table 3, the underlying disease was very different, with MPA/RLV predominating in Japan, although the overall occurrence of PRV was similar in Japan and the UK. ENT and neurological involvement were much less common in Japan. ANCA status was also different between Japan and the UK; positive MPO-ANCA was 91.1 versus 55.6%, and positive PR3-ANCA 0 versus 33.3%. Thus, PRV patients with cANCA/PR3 and/or WG seem to be much less common in Japan than the UK.

Outcome and Treatment

To improve the survival rate and renal prognosis in patients with AAV/PRV, the therapeutic methods may be different between Japan and Europe/USA because clinical phenotype and features were very different among

Table 3. Comparison of epidemiology and clinical features of ANCA-associated renal vasculitis between Japan and the UK

	Japan (Miyazaki)	UK (Norfolk)	p
Male/female	24/32	13/14	
Mean age, years	70.4	63.5	
Incidence, /million			
Total	14.8 (10.8–18.9)	12.2 (8.0–17.7)	
MPA/RLV	14.8 (10.8–18.9)	5.0 (2.4–8.8)	
WG	0	5.8 (2.9–9.4)	
CSS	0	1.4 (0.3–3.9)	
ENT	1 (1.8%)	18 (66.6%)	<0.001
Respiratory	23 (41.1%)	11 (40.7%)	NS
Nervous	3 (5.4%)	8 (29.8%)	<0.02
Gastrointestinal	2 (3.6%)	3 (11.0%)	NS
MPO-ANCA	51 (91.1%)	15 (55.5%)	<0.001
PR3-ANCA	0	9 (33.3%)	<0.001
Negative ANCA	5 (8.9%)	2 (7.4%)	NS

these countries. Although the combined therapy with cyclophosphamide and glucocorticoids is recommended as the standard of care in remission induction therapy in Europe and the USA, only one fourth to one third of PRV/RPGN patients have received these drugs in Japan [33, 43]. Both patient and renal survival rates among Japanese PRV patients (RLV + MPA + WG) recently improve to 84.1 and 83.7% at 12 months, and to 79.1 and 78.5% at 24 months, respectively [33]. A major cause of death is indirectly related to vasculitis and mostly consists of treatment-related infectious complications. This could be because a high proportion of Japanese patients are elderly and/or dialysis-dependent at presentation with MPA/RLV predominating in Japan [43]. In the Japanese clinical guideline for RPGN based on the questionnaire survey [33], milder immunosuppressive treatment such as an initial oral prednisolone dose reduction (0.6~0.8 mg/kg/day) with or without immunosuppressant is recommended for older and/or dialysis-dependent patients.

On the other hand, randomized clinical trials of new therapies for AAV have been performed in Europe and the USA. On the principle that more severe disease requires more aggressive therapy, EUVAS devised a system for subgrouping AAV presentations, for example, based on the severity of renal impairment, for different regimens [44]. Results of such trials are very informative and might lead to consensus recommendations on how to AAV/PRV should be treated depending on the types, the disease severity and age.

Laboratory Investigations: ANCA Epitopes in the Japanese Population and ELISA Evaluation

Epitopes of MPO-ANCA in Vasculitis in the Japanese Population

MPO-ANCA-Associated Vasculitides in Japan

ANCA are found in a high percentage of patients with WG, MPA, and CSS and are used as diagnostic markers for these diseases, which are also termed AAV. Furthermore, MPO-ANCA has been demonstrated to be a good marker for the diagnosis of these disorders. The titer of MPO-ANCA is correlated with the activity of autoimmune, necrotizing, crescentic glomerulonephritis. In addition, a good correlation between the extent of crescent formation and the MPO-ANCA titer has been demonstrated [10]. However, a low titer of MPO-ANCA is found in the sera from some patients with active crescent formation, and conversely, high titer can be found during the remission stage in Japanese patients. Therefore, it seems that the titer of MPO-ANCA is not always correlated with the activity of the disease due to the difference in reactivity of MPO-ANCA to the MPO molecule. Such differences in reactivity suggest differences of binding to MPO epitopes by MPO-ANCA. The inconsistency of MPO-ANCA titer in primary systemic vasculitis (PSV) may be attributable to differences in epitopic specificity by MPO-ANCA between patients.

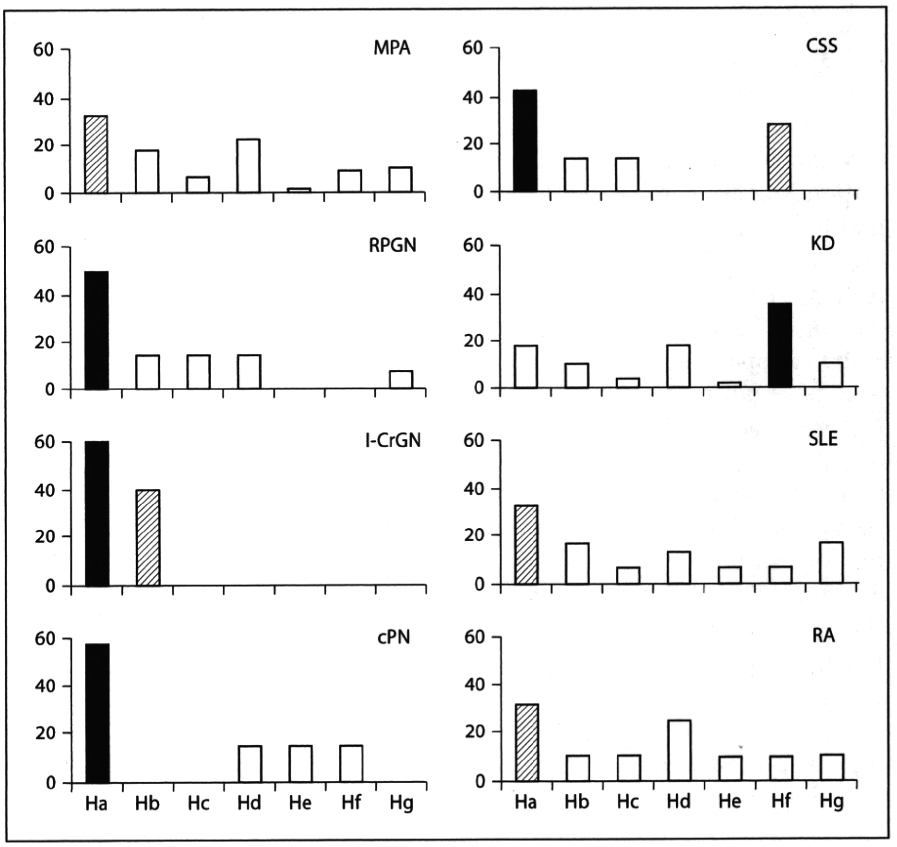

Fig. 2. Frequency of epitope sites of MPO-ANCA in the serum of patients with vasculitis. Incidence in each vasculitis shows relative ratio (%) in all epitopes reacted with MPO fragments [45].

Analyses of the Epitopes in MPO-ANCA in the Japanese Population

Epitopes on MPO recognized by MPO-ANCA from patients with MPO-AAV in the Japanese population have been analyzed using recombinant MPO fragments set using deletion mutants of MPO composed of eight fragments of the heavy-chain subunit, and two fragments of the light chain subunit expressed in *Escherichia coli* [11].

Epitope analysis may also explain the occurrence of MPO-ANCA in different vasculitic syndromes. The sera of 148 MPO-ANCA-positive patients from four vasculitic syndromes (MPA, classic polyangiitis nodosa, CSS and KD) and from patients with RA and SLE are applied to the epitope analysis. The sera have been collected by the Intractable Vasculitis Research Project Group in Japan.

In PSV, MPO-ANCA are markers for diagnosis and have been implicated in pathogenesis of vasculitis. Although high MPO-ANCA titers are associated with an increased risk of disease activity, MPO-ANCA titers do not necessarily correlate with disease activity or vasculitic syndrome. The severity of the diseases in MPA with renal involvement is correlated with particular epitopes of MPO-ANCA recognizing the N or C terminus of the MPO heavy chain [9]. The epitopes recognized by MPO-ANCA from sera of patients with four vasculitic syndromes (MPA, cPN, CSS, KD) and from patients with RA and SLE in hospitals at Juntendo University, Kyorin University, Kyoto University, Tokyo Medical School, Fujita Medical Health University, and Hiroshima City in Japan, members of the project funded by the Ministry of Health, Labour and Welfare, have been analyzed [45].

No serum showed epitopes La and Lb of light chain MPO, and sera of 68.6% of patients showed a positive reaction to one or more epitopes of heavy-chain MPO. An analysis of the binding level showed that MPA sera mainly reacted to the Ha epitope at the N terminus of the MPO heavy chain, CSS sera reacted to the Ha and Hf epitopes close to the C terminus of the MPO heavy chain, and KD reacted mainly to Hf, whereas SLE and RA sera reacted to all epitopes. These results suggest that MPO-ANCA recognizing specific regions of the N terminus of the MPO H chain confer an increased risk of vasculitis such as MPA and CSS. Furthermore, the epitopic specificity of MPO-ANCA differentiates vascu-