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# A population-based study of Takayasu's arteritis in eastern Denmark

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**Key words:** Takayasu's arteritis, vasculitis, epidemiology, incidence, cardiovascular events

## ABSTRACT

**Objectives.** To evaluate the annual incidence of Takayasu's arteritis (TA) in eastern Denmark and to describe the clinical course of Danish TA patients.

**Methods.** All patients living in the eastern part of Denmark and registered with a first-time hospital discharge diagnosis of TA between 1990 and 2009 were identified. The TA diagnoses of the identified patients were confirmed by medical records review.

**Results.** A total of 19 TA patients (3 males and 16 females) were included in the study. Two patients were of Asian origin, while 17 were Caucasians. The median patient age at the time of the TA diagnosis was 36 years (range: 19–66 years), and the median time interval between the onset of symptoms attributable to TA and the diagnosis of the disease was 11 months (range: 1–50 months). The estimated mean annual incidence of TA was 0.4 (95% CI: 0.25–0.62) per million. No deaths occurred during a median follow-up period of 11.5 years (range: 0.5–19.5 years). Eleven patients (58%) experienced one or more serious vascular events due to TA. Among these, eight patients developed their vascular complications before the vasculitis diagnosis was established.

**Conclusion.** In the current cohort, serious vascular events affected a large proportion of patients before the TA diagnosis was made or during follow-up. The incidence of TA in Denmark seems to be comparable to the incidence in other regions of Europe.

## Introduction

Takayasu's arteritis (TA) is a rare large-vessel vasculitis of unknown aetiology. The chronic granulomatous inflammation characteristic of the disease predominantly affects the aorta, its primary branches, and the pulmonary arteries, resulting in the formation of aneurysms and luminal stenoses. Severe clinical manifestations of TA typically reflect

end-organ ischaemia and include ischaemic heart disease, cardiac failure, cerebrovascular events, reno-vascular hypertension, and claudication (1). The incidence of TA in Europe has been evaluated in few studies, with incidences reported in the range of 0.4–1.3 per million (2–5). In this population-based study, we assessed the incidence of TA in the eastern part of Denmark during the period 1990–2009. Furthermore, we evaluated the clinical course of Danish patients with TA.

## Patients and methods

Patients diagnosed with TA between January 1, 1990 and December 31, 2006 were identified by means of The Danish National Hospital Register (NHR). This register was established in 1977 and keeps information on all admissions to non-psychiatric hospital departments in Denmark (6). Since 1994, in-patient data has been supplemented by data on outpatient hospital contacts. Each hospital contact initiates a record, which contains the personal identification number of the patient (unique to each Danish citizen), a hospital department code, dates of admission and discharge, a primary discharge diagnosis, and supplementary diagnoses. Diagnoses were coded according to a Danish version of the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and according to the ICD-10 thereafter. A search was performed for patients living in the eastern part of Denmark and registered in the NHR with a first-time discharge diagnosis of TA (modified ICD8: 446.90 and 446.91; ICD10: M31.4) between 1990 and 2006. In the search, the eastern part of Denmark was defined as the Capital region, the Zealand region, the Island of Bornholm, and Christians Island. This area is populated by approximately 2.4 million inhabitants, corresponding to almost half of the Danish population. We did not have access to updated in-

Competing interests: none declared.

**Table I.** Clinical characteristics of 19 patients diagnosed with Takayasu's arteritis (TA) in the eastern part of Denmark between 1990 and 2009 and followed throughout 2009.

Year of diagnosis	Sex	Age	Diagnostic delay <sup>1</sup> months	TA subtype <sup>2</sup>	Vascular events and/or vascular surgery <sup>3</sup>	Vascular events before TA diagnosis
1990	F	23	1	I	Stroke	Yes
1992	F	36	14	Iib	Aortic arch reconstruction	No
1993	M	36	15	Iib	No	–
1993	F	25	12	I	No	–
1994	F	32	24	I	No	–
1995	F	25	47	I	No	–
1995	F	45	3	I	Stroke	Yes
1996	F	23	1	IV	Renal artery stenting	Yes
1996	F	42	1	I	No	–
1998	F	20	4	Iia	No	–
1999	F	19	1	Iib	No	–
2004	F	36	25	V	Myocardial infarction thrice	Yes
2004	M	49	11	V	Coronary artery stenting, aorto-bifemoral grafting	No
2005	F	48	50	I	Stroke	Yes
2008	F	66	12	I	No	–
2008	F	39	13	Iia	Coronary artery stenting	Yes
2008	F	56	9	V	Aorto-bifemoral grafting	No
2009	M	41	4	IV	Renal artery stenosis	Yes
2009	F	21	5	IV	Claudication, renal artery stenting	Yes

<sup>1</sup>Time interval between first symptom attributable to TA and diagnosis of the disease; <sup>2</sup>As defined in text; <sup>3</sup>Either before the diagnosis of TA was established or during follow-up.

formation in the NHR for patients diagnosed between January 1, 2007 and December 31, 2009. Therefore, we identified all patients registered from 2007 to 2009 with a first-time TA diagnosis in the hospital contact lists of the Department of Rheumatology at Rigshospitalet, Copenhagen University Hospital. During this period, all patients of eastern Denmark with suspected or established TA were routinely referred to our tertiary care centre, which provides treatment for patients with systemic vasculitides in the region. The TA diagnoses of the identified patients were evaluated by medical records review, and patients who met the modified Ishikawa's criteria for TA (7) were included in the study.

For the included patients, the subtype of TA was determined based on the pattern of large-vessel disease involvement (Type I: branches from the aortic arch; Type Iia: the ascending aorta, aortic arch and its branches; Type Iib: the ascending aorta, aortic arch and its branches, and the thoracic descending aorta; Type III: the thoracic descending aorta, abdominal aorta, and/or renal arteries; Type IV: the abdominal aorta, and/or renal arteries; Type V: the com-

bined features of both type Iib and IV) (8). Furthermore, we registered the date of initial symptoms attributable to TA, the date of the TA diagnosis, data on treatment, and information regarding vascular complications experienced by the patients before and after the diagnosis of vasculitis. The patients were followed for vascular events and death until the end of 2009.

#### Statistics

The mean annual incidence of TA was calculated as the observed number of TA cases during the study period divided by the cumulated population in eastern Denmark during 1990–2009. The period prevalence was calculated as the observed number of cases in the study divided by the average population in eastern Denmark between 1990 and 2009. The 95% confidence intervals (CI) were calculated assuming a Poisson distribution of the observed cases.

#### Results

In total, thirty-nine patients with a TA diagnosis were identified by means of the described search strategy. Twenty of the identified patients did not meet the diagnostic criteria for TA, leaving

19 patients diagnosed with TA during 1990–2009 for further analyses (3 males and 16 females). None of the excluded patients presented with symptoms suggestive of TA, and other diagnoses were established during follow-up in all cases. Clinical characteristics and cardiovascular events of the TA patients are summarised in Table I. Two patients were of Asian origin, while 17 were Caucasians. The median age at the time of TA diagnosis was 36 years (range: 19–66 years), and the median time interval between the onset of symptoms due to TA and the diagnosis of vasculitis was 11 months (range: 1–50 months). The median duration of follow-up was 11.5 years (range: 0.5–19.5 years). Four patients developed permanent work disability after the diagnosis of TA. All patients were alive by the end of the study period.

Fifteen patients (79%) received either oral prednisolone or high-dose intravenous corticosteroid therapy as the initial treatment for TA. If this failed to suppress disease activity, other immunosuppressive agents were used. Thus, 9 (47%) patients were treated with methotrexate, 4 (21%) received cyclophosphamide, 5 (26%) received azathioprine, 3 (16%) were treated with mycophenolate mofetil, and 5 (26%) were given anti-tumour-necrosis-factor- $\alpha$  therapy. Four patients (21%) never received any immunosuppressive therapy, as disease activity could not be demonstrated after the TA diagnosis was made. Nine patients (47%) required anti-hypertensive medication. None had uncontrollable hypertension. Eleven patients experienced one or more serious vascular events during their course of illness (Table I). In eight of these patients, the vascular events occurred before the TA diagnosis was established. Six patients underwent vascular surgical procedures due to critical vessel stenoses.

During the period 1990–2009, the mean annual incidence of TA in the eastern part of Denmark was 0.4 (95% CI: 0.25–0.62) per million, and the prevalence was 8.0 per million (95% CI: 5.08–12.48). Twelve patients were diagnosed with TA before the age of 40 from a population of 1.0 million, and

the mean annual incidence of TA was 0.6 per million (95% CI: 0.36–1.12) for persons <40 year of age.

### Discussion

In this population-based study, we found an incidence of TA in the eastern part of Denmark, which is comparable to incidence estimates reported from other regions of northern Europe (3–5), but slightly lower than that reported from a range of non-European countries (9–11). As in previous investigations, we observed that the diagnosis of TA is frequently preceded by a substantial diagnostic delay (12–17), and that TA patients often experience significant cardiovascular morbidity prior to the establishment of the vasculitis diagnosis (11–14, 18).

Of note, 7 out of 19 (37%) of our patients were more than 40 years of age at the time of diagnosis. In other studies, the proportion of TA patients with disease onset/diagnosis after 40 years of age was 9%(19), 13%(13), 14%(16), 15%(15), 17%(14), 23%(17), and 32%(12), respectively. Furthermore, 50% of the patients were more than 40 years of age at time of the TA diagnosis in a recent population-based investigation from the UK (5). These findings all emphasise that age >40 years should not be used to exclude the possibility of TA in patients with suspected large-vessel vasculitis.

Varied mortality figures have been reported in different TA studies (20). In recent investigations, 10-year survival rates of 73.0%(19), 87.2%(17), and 90.8%(12) were found. Among our patients, no fatalities occurred during a median follow-up period of 11.5 years. Severe hypertension, severe functional disability, and evidence of cardiomegaly, cardiac failure, or left ventricular hypertrophy were previously identified as risk factors for death and major cardiovascular event in TA (18). Such clinical features were not prominent in our cohort, and this may in part account for the relatively good outcome observed. In a French study, the mortality differed between white, black and North African TA patients with 10-year survival rates of 95%, 100% and 67%, respectively (12). Interestingly, the Type V disease pattern was seen in 65%

of North African patients, but only in 38%–40% of other patients. In a study of 110 Mexican TA patients, 69% presented with Type V disease, and the 10-year survival was 73% (19). Bicakcigil *et al.* studied 248 Turkish TA patients, 51% of whom had Type V disease, and found a mortality of ~5% during a mean follow-up period of 7.2 years (16). In our study, the pan-aortic Type V variant of TA affected as few as 3 out of 19 patients (16%). Together, these findings suggest that the extent of large-vessel disease involvement may also be of prognostic importance in TA.

The combined use of a national hospital discharge register and medical files review is a strength of the present study. Between 1990 and 1993, outpatient hospital visits were not registered in the Danish NHR. Therefore, TA patients diagnosed in eastern Denmark and followed without any in-patient registrations during 1990–1993 would not have been identified by means of our search strategy. The number of missed cases is, however, likely to be very limited. TA is not covered by a screening programme in Denmark, and since most Danish doctors do not have great experience with diagnosing the disease, some cases of TA may have been misclassified or not recognised at all during the study period. Therefore, even though comparable incidence rates have been reported from other European countries (2–5), it seems probable that the true incidence of TA in Denmark is somewhat higher than assessed in the current investigation.

In conclusion, our data confirm that TA is a rare disease in northern Europe and that a substantial diagnostic delay often precedes the diagnosis of vasculitis. Increased clinical awareness of the disease is needed to minimise the duration of diagnostic uncertainty and to reduce the risk of vasculitis-induced large-vessel damage in TA.

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