Takayasu Aortoarteritis

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INTRODUCTION

Takayasu arteritis (TAK) is a rare form of primary systemic vasculitis which appears commoner in the Far East than in Europe or N America. It particularly involves the aorta and the main branches coming from that, so the symptomatology is markedly different from that of the small/medium vessel vasculitides. The pathology includes giant cells but unlike the classical giant cell arteritis seen in temporal arteritis, which affects older populations and is rare under the age of 60, TAK affects younger age groups, including children. However, just as Temporal Arteritis is commonly associated with Polymyalgia Rheumatica, TAK has been described as starting with a rather non-specific systemic illness with fever and muscle pains. This has promoted interest in the role of infection in the aetiology and an association with tuberculosis has been much discussed. It also shows a strong female preponderance. Thus the stereotype has built up that TAK is a disease of young, oriental females, with probable genetic and infectious strands to the aetiology.

TAKAYASU IN ENGLAND

TAK is rare in the UK and we have only seen about one case per year over the past 2 decades at our centre. There is a significant ethnic minority population in Birmingham, with both a small Chinese and a large S.Asian group (coming from the Indian subcontinent). However our small TAK series was predominantly Caucasian, with an equal number of males. They did not fit the textbook paradigm in other ways either. One middle-aged female presented with a long polymyalgic phase before a pulse inequality was detected – but others presented acutely to the vascular surgeons with occlusive disease. The latter patients also challenged the earlier concepts that the polymalgic phase is inflammatory while the occlusive phase represents late fibrotic scarring. We were fortunate to obtain biopsy material during carotid bypass surgery from the first such case, seen in 1982. This showed a complete absence of scarring in the vessel wall but there were dense, focal lymphocytic infiltrates. These consisted almost exclusively of CD8 +ve T cells, leading us to speculate on the role of T-cells in the aetiopathogenesis.[1] The absence of phagocytic or other inflammatory cells was also consistent with the absence of any acute inflammatory response in this patient, who showed a normal ESR and CRP at presentation and at two later relapses.

TAKAYASU IN INDIA

TAK appears to be far commoner in India, although accurate epidemiology is very difficult. One group with a major interest reckons to see around 50 new cases annually at a major government hospital in Mumbai.[2] This compares to estimates of 100 new cases per year for the whole of Japan, indicating that the incidence is at least as high as in that country. The cardiovascular group in Kolkata has published a monograph based on a series of 650 cases[3] while most rheumatologists have a series of at least a few cases. There has been much speculation about the role of mycobacteria in the aetiology of TAK as seen in India. M.tb was seen in a significant proportion of cases in the two large series quoted – but it is still a common infection in India. It remains possible that this is simply co-incidence of common infection with a rare vasculitis. Another possibility is that some aspects of the pathology share common features. The Mumbai group have noted major para-aortic lymphadenopathy as a common feature at PM.[4] The enlarged nodes may show caseation apparently typical of tuberculosis, yet staining and culture are negative for M.tb. It remains to be determined whether this is truly a feature of TAK or represents a mixed pathology related to inflammatory vasculitis plus infection.

DIAGNOSIS/CLASSIFICATION

In patients presenting with a vessel occlusion, the clinical diagnosis is not difficult. The ACR criteria can be useful in such cases.[5] However those with vague systemic illness and pains, or with hypertension secondary to renal artery stenosis, may take a lengthy time before positive investigations reveal the correct diagnosis. The gold standard to confirm the diagnosis is aortography. The problem is that imaging the vessel lumen can only show scarring. MRI has the potential to show the state of the vessel wall and thus reveal inflammatory thickening at an earlier stage. It has been suggested that this should be added to the investigation regime in cases presenting with a PUO or similar systemic illness, a luxury restricted to selected centres.

The Japanese group studying this disease have also produced a set of diagnostic criteria, based on the presence of 2 major or one major plus at least two minor criteria.[6] These have been slightly modified for use in India.[7]

Another approach to study the disease is classification based on disease distribution.[8] Some cases appear restricted to the thoracic aorta and branches, while others predominantly involve the abdominal part, leading to renal disease and lower limb ischaemia. The former appears more frequent in Japan and N America, while the latter (together with the type V involving all sections of the aorta) has been described more commonly in India. These observations suggest that there may be real differences in the disease pattern across the world, possibly reflecting different genetic or infectious contributions to aetiopathogenesis. Further, more detailed, epidemiological studies are required to confirm the basic observations before this can be taken further.

ASSESSMENT OF ACTIVITY

Detailed assessment of disease extent and activity are essential to follow both the log term outcome and the response to therapy in TAK. Validated instruments to do this, such as BVAS[9] and VDI[10] are established for the less uncommon small/medium vessel vasculitis and have played a key role in recent international controlled clinical trial in ANCA-associated vasculitis.[11, 12] However, experience has shown that these are less useful in TAK. The main problem here is assessing activity in a disease where so much of the pathology is located in deep-seated vessels, progressing at a slow pace and not necessarily associated with any acute phase response. The need is to develop techniques that will allow activity to be assessed independently of acute clinical events, such as vessel occlusion. It is hoped that assessment of inflammation in the vessel wall by MRI or PET may provide this – and detailed studies of the role of these expensive techniques are proceeding in the UK and the USA. The establishment of a gold standard for activity, even if not widely available, should provide the necessary anchor for clinical studies.

IRAVAS has been wrestling with the development of clinical indices to study TAK for some time. Initial experience showed the inability of BVAS to capture disease activity satisfactorily. The attempt to adapt BVAS into an index specific to TAK failed when it proved impossible, even in a group with wide experience of the condition, to achieve consensus on items to include. IRAVAS thus turned its attention to developing a disease extent index. This approach has been useful in detailing the varied pattern of disease expression and outcome in Wegeners granulomatosis, another relapsing form of systemic vasculitis.[13] It proved easier to obtain consensus on items for inclusion here and the initial version is currently being validated. The DEI.Tak generated contains 59 items in 11 organ-based systems. This is fewer than the BVAS and differs from the latter also in the detailed focus on CVS aspects. The data sheet also includes an acute phase test and the physicians global opinion on activity. It is now in use to determine the extent and pattern of disease seen by rheumatologists in India.

SPECTRUM OF TAK PRESENTING TO RHEUMATOLOGISTS IN IRAVAS

An initial analysis has been presented on 143 patients, approximately half of those currently being followed by the members of the IRAVAS group.[14] These cases show a sex ratio of 1.5F: 1M, lower than the Japanese but consistent with other Indian series. The DEI.Tak analysis showed that ~40% had systemic symptoms, which was fever in half – with musculo-skeletal symptoms or weight loss being far less common than in AA.SV. This contrasts with pulse loss, seen in c80%. CVS involvement was the major feature throughout, with bruits being recorded in over 40%, particularly from the carotid – although the very specific sign of carotidynia was exceptionally uncommon. No correlation was found between ESR and any stage of pulse involvement (bruit, pulse loss or claudication). Renal bruits were detected in 12% but renal involvement was noted in c40%. This was predominantly hypertension and half of these had renal artery stenosis. These data are consistent with reports of the frequent occurrence of Type IV (lower aortic) and Type V (total aortic) patterns of disease in India. They emphasize again the marked

differences between this form of giant cell arteritis and the well-studied features of small/medium vessel vasculitis.

There is no established "best therapy" for TAK and a spectrum of drugs was used to treat these patients in practise. The large majority had received steroids but many had also had immuno-suppressive drugs, supporting the developing consensus that steroids are symptomatic rather than curative in aorto-arteritis. Methotrexate was the most frequent but Azathiaprine is also used and Mycophenolate has been found easy to use in Indian practice. Cyclophosphamide, which we have found useful in the UK, has been avoided in India due to the risks of infertility in these younger patients. Infliximab has been tried in a handful of subjects.

CONCLUSION

Takayasu aorto-arteritis remains an understudied disease form of primary vasculitis. There remain real difficulties in establishing the diagnosis before pulse loss produces major clinical problems. Standardised assessment of disease activity also hinders a rational approach to therapy and there are currently no RCT's in this disease. The development of the DEI.Tak is an attempt to remedy this. It will allow standardised assessment of outcome in this disease. It can also be used to collect epidemiological data which can address questions like the patterns of involvement in various countries, providing new insights into aetiologic factors. Large standardised data banks collected by collaborative groups such as the IRAVAS one can both combine across continents to stimulate clinical interest in TAK and link with laboratory scientists to develop better disease markers.

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