Pediatr Nephrol (1998) 12:668–675

Pediatric Nephrology

Practical pediatric nephrology

A review of Takayasu's arteritis in children in Gauteng, South Africa

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Received December 10, 1997; received in revised form March 13, 1998; accepted March 16, 1998

Abstract. We have reviewed 31 patients with Takayasu's arteritis followed at two pediatric nephrology units in Gauteng, South Africa over a 15-year period. There were 25 black patients, 4 white, and 2 of mixed race. The mean age at diagnosis was 8.42±3.59 (range 2.4–14.5, median 8) years. The most common presenting sign was hypertension, followed by cardiac failure, bruits, and absent pulses. The Mantoux test was strongly positive in 27 patients (90%, control population 5%). Markers of activity included a raised erythrocyte sedimentation rate (23 patients) or Gallium single photon emission tomography (positive in 12 of 16 patients). Angiography revealed type II (abdominal aorta) and III (arch plus abdominal aorta) lesions to be most common (11 in each group). All patients received antituberculous therapy and most low-dose aspirin for its antithromboxane effect. Corticosteroids and further immunosuppression were used to control disease activity. We added total lymphoid irradiation (TLI) or cyclophosphamide. Twenty-six patients in all received further immunosuppression, with 13 patients in each group. Results were similar in the two groups, with similar pre- and post-therapy systolic blood pressures and creatinine clearances. Two patients in each group relapsed, 3 died in the TLI group and 2 in the cyclophosphamide group. Surgical intervention, usually in the quiescent phase, consisted mainly of renal autotransplantation. Because of the problems with TLI and 2 patients with papillary carcinoma of the thyroid with long-term follow-up, we no longer use TLI. We have shown that with active medical and surgical intervention the aggressive course of this disease in children can be modified.

Key words: Takayasu' arteritis – Tuberculosis – Gallium single photon emission tomography – Corticosteroids – Cyclophosphamide – Total lymphoid irradiation – Autotransplantation

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Introduction

Takayasu's arteritis is a chronic inflammatory disease involving primarily the aorta, its proximal branches, and occasionally the pulmonary arteries, and results in stenosing, occlusive, or aneurysmal lesions. It has also been termed pulseless disease, aortic arch syndrome, occlusive thromboaortopathy, and non-specific aortoarteritis [1]. The first clinical case reported was probably by Savory in 1856, but current concepts come from Takayasu's description in 1908, who reported unusual ocular findings in young women, which were associated with absent pulses in the upper limbs [2]. The disease is widely prevalent in South Asia and Central America, but a worldwide distribution has been documented [3]. Initial South African documentation was by Isaacson et al. in 1959 [4], with successive reports by Isaacson and Schnier in 1961 [5] and Schrire and Asherson in 1964 [6]. It occurs predominantly in young women, with a peak incidence between 10 and 25 years, but may occur from early childhood to late adulthood [7].

The etiology and predisposing factors of Takayasu's arteritis are as yet unknown, although infections such as tuberculosis (TB) and an autoimmune component have been invoked [8–11]. The clinical presentation is widely heterogeneous and involves two stages: (1) an initial inflammatory process or 'prepulseless phase' with variable systemic manifestations occurring, followed by (2) a later 'pulseless phase' with multiple arterial occlusions producing symptoms of cerebral, visceral, or extremity ischemia [12–14].

The natural history and optimum therapy of Takayasu's arteritis are as yet uncertain. Widely varying mortality rates are documented, but obviously depend on the severity of the disease and therapeutic strategies. Factors related to increased mortality include hypertension, Takayasu's retinopathy, arterial aneurysm, and aortic regurgitation [15–17]. Therapy is multifaceted, including medical and surgical intervention. Medical therapy consists mainly of immunosuppressives such as corticosteroids and cytotoxics (e.g., cyclophosphamide)

[18–22]. In our center total lymphoid irradiation (TLI) has been used to control disease activity, but had not been compared with cyclophosphamide [23]. Surgical intervention to improve organ perfusion is often required, subsequent to vascular damage [24].

Patients and methods

Patients assessed were those referred to and followed up at the pediatric nephrology units of the Johannesburg and Chris Hani Baragwanath Hospitals in whom Takayasu's arteritis was diagnosed. Data from the two units were analyzed together, i.e., as coming from one unit. Both units are, in fact, attached to the University of the Witwatersrand.

All patients were fully evaluated, including a history, clinical examination, and transfemoral angiography. Serological tests, including syphilis, antidouble-stranded DNA antibody, antinuclear factor, rheumatoid factor, and antineutrophil cytoplasmic antibody were performed to exclude other collagen vascular disorders. Further investigations included: Mantoux tests (5 U intradermal purified protein derivative), which were performed on all, and measurement of erythrocyte sedimentation rate (ESR), often with a Gallium single photon emission tomography (SPECT) scan (coronal, transaxial and sagittal views), to measure activity [23]. Serial serum creatinine measurements and dimercaptosuccinic acid scan to assess differential function where appropriate, were performed. The extent of vascular involvement, determined by angiography, was defined according to the accepted classification [25]. Some patients were also assessed by magnetic resonance imaging (MRI). Where possible, specimens were also assessed histologically.

Treatment principles. Patients with congestive cardiac failure were managed according to accepted treatment regimens. Hypertension was ameliorated using standard antihypertensives, but angiotensin converting enzyme (ACE) inhibitors were only used when bilateral renal stenosis had been excluded. If the hypertension was intractable with bilateral renal arterial stenosis, ACE inhibitors were used very cautiously, with frequent checks of maintenance of renal function. All patients received antituberculous therapy, and most also received low-dose aspirin for its anti-thromboxane effect. Steroids were commenced at a daily dose of 2 mg/kg and gradually tapered according to clinical response. Ten patients included in this review have been described elsewhere [23, 26].

As a result of previous poor outcome in patients in our region [27], a more-aggressive immunosuppressive approach was adopted in our units. Patients were managed with either TLI or cytotoxic chemotherapy (cyclophosphamide). All but 2 patients had the treatment allocation selected by random numbers, and both units were allocated treatment from the same batch of random numbers. The TLI regimen was modelled on a wide-field low-dose irradiation schedule, previously used as an immunosuppressive pretransplant work-up [28]. This therapy was also subsequently used in some of our patients with systemic lupus erythematosus [29], and has been used by Strober et al. [30].

The technique used for TLI has been described previously [21, 28]. Prior to each treatment, full blood and differential counts were performed. Treatment was interrupted if the total white cell count was less than 1.2×10^9/l, the neutrophil count less than 0.8×10^9/l, or the platelet count less than 50×10^9/l. A treatment delay was also instituted with any evidence of infection.

Patients receiving cyclophosphamide were given an initial IV bolus of 500–750 mg/m^2, and then an 8-week course of oral therapy at 2–3 mg/kg, starting 2 weeks after the IV cyclophosphamide. Some patients were not given the initial IV bolus. Instead, the course consisted of an 8-week oral dose of 3 mg/kg per day cyclophosphamide. The dosage was adjusted to maintain the white cell count above 3×10^9/l. Surgical intervention was instituted to improve organ perfusion in patients showing features of organ dysfunction secondary to ischemia related to vascular occlusion.

Statistics. Where appropriate, Student t-test (two-tailed) was used to assess comparative data in matched groups. Two-tailed Fisher exact test was used to compare results showing absolute end points, e.g., mortality.

Results

The clinical and treatment profiles of the 31 patients retrospectively evaluated are shown in Fig. 1 and Table 1. The mean age of our patients (13 males, 18 females) was 8.42±3.59 years (range 2.4–14.5, median 8 years); 25 patients were black, 4 white, and 2 of mixed race. There were no Asian children. The most common presenting sign was hypertension, with only 2 patients presenting with constitutional symptoms, e.g., fever, arthralgia (Fig. 1).

The Mantoux test was positive in 27 patients (90%). In the majority of these patients it was strongly positive, i.e. >15 mm or ulcerated. This strongly positive reaction occurs in 5% of the control population. Three patients were receiving treatment for pulmonary TB; 1 had prior therapy for TB and 3 had a family history of TB at the time. The ESR or C-reactive protein was elevated in 23 patients. Gallium SPECT scintigraphy was performed in 16 patients and was positive in 12.

We classified our patients into five types according to the extent of vascular involvement shown angiographically: types I–IV as originally proposed by Ueno et al. [31] and modified by Lupi Herrera et al. [32], with type V added in 1988 [26] (Fig. 2). Sedation for angiography consisted of midazolam plus anesthetic (or ketamine in younger patients). Patients were divided as follows; 11 had type II alone, 11 had type III alone, 4 had type IV, and 5 had type V disease. The renal arteries with resultant renovascular hypertension were most frequently involved. Eleven patients had unilateral artery involvement and 15 had bilateral vessel involvement. There were no documented complications following angiography.

All our patients received antituberculous therapy, and all except 2 received corticosteroids. Further immunosuppressive therapy to halt disease progression consisted of TLI or cyclophosphamide. Twenty-six patients were

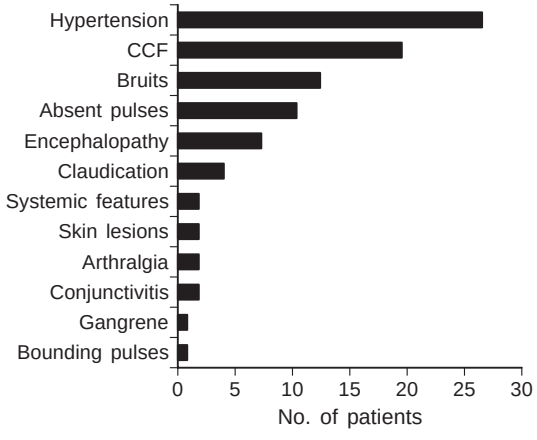

Fig. 1. Presenting clinical features in the 31 patients with Takayasu's arteritis. *CCF,* Congestive cardiac failure

Table 1. Angiographic findings, treatment, and outcome in 31 patients with Takayasu's arteritis

Patient no.	Vascular involvement	Immuno-suppression	Surgery	Outcome
1	Stenosis AA, left RAS	TLI	Bilateral autotransplants	Alive
2	Stenosis AA, left RAS, iliacs	Cyclo	Saphenous interposition left renal artery	Alive
3	Stenosis AA, bilateral RAS	Cyclo (3/52)	Right autotransplant clotted	Died (hypertension)
4	Stenosis AA, right RAS	TLI	Right autotransplant	Alive
5	Left CC, right RAS	Nil	Failed renal arterystent – nephrectomy	Alive
6	Left CC, bilateral RAS	Cyclo	Right autotransplant/left nephrectomy	Alive
7	Right+left subclavian bilateral RAS	Cyclo	Right nephrectomy	Alive
8	Coarctation arch+ascending aorta, external iliacs	Nil	Repair coarctation	Alive (histology – Takayasu's)
9	Aneurysm arch, right subclavian, carotid	Cyclo	Nil	Alive
10	Aneurysm AA, bilateral RAS	Nil	Bilateral goretex grafts – blocked left autotransplant	Died (graft erosion)
11	Ascending aorta, bilateral iliacs, pulmonary artery	Cyclo	Nil	Alive
12	Stenosis AA, bilateral RAS	Nil	Nil	Alive
13	Aneurysm ascending aorta, right RAS	Cyclo	Nil (refused)	Alive
14	Stenosis AA, bilateral RAS	Cyclo	Right axillo-femoral bypass (occluded)	Died (hypertension)
15	Stenosis AA, bilateral RAS	Nil	Nil	Died (hypertension)
16	Left subclavian, bilateral RAS	TLI	Bilateral autotransplant – failed	Cadaver transplant Pap. ca. thyroid
17	Stenosis AA, left RAS, pulmonary artery, hypoplastic right kidney	TLI	Angioplasty left renal artery – failed	Died post cadaver transplant
18	Right carotid+brachiocephalic left RAS	Cyclo	Left autotransplant	Alive. Relapse → TLI
19	Bilateral carotids, bilateral RAS, external iliacs	TLI	Emergency bilateral autotransplant	Alive
20	Stenosis AA, bilateral RAS	Cyclo	Bilateral autotransplant/ goretex patch aorta	Alive
21	Aneurysm AA, right RAS, no left renal artery	Cyclo	Left autotransplant – failed	Alive (22 weeks' pregnant)
22	Aneurysm arch+descending aorta, AI, pulmonary artery	Cyclo	Nil	Alive
23	Aneurysm arch, thoracicaorta+AA	TLI	Nil	Alive
24	Aneurysm arch+AA, bilateral RAS	TLI	Bilateral autotransplant	Alive
25	Stenosis AA, bilateral RAS	TLI	Bilateral goretex grafts – blocked	Cadaver transplant Alive
26	Aneurysm AA involving right renal artery	Cyclo	Right nephrectomy (later left autotransplant)	Relapse TLI Left autotransplant Alive
27	Aneurysm arch+descending aorta, fem-pop. occluded	TLI	Later right autotransplant	Relapse→Cyclo Right autotransplant Alive
28	Bilateral pulmonary arteries, pulmonal HT	TLI	Nil	Died (CCF)
29	Bilateral subclavian, left RAS	TLI	Left renal arterystent failed/ left autotransplant	Alive
30	Left RAS, right renal artery thrombus	TLI	Right nephrectomy/left autotransplant, Failed	Cadaver transplant, Died. EBV hemophagocytic syndrome
31	Aneurysm arch, left RAS	TLI	Left autotransplant failed/ right autotransplant	Alive. Term pregnancy – normal baby

AA, abdominal aorta; AI, aortic incompetence; CC, common carotid; Cyclo, cyclophosphamide; TLI, total lymphoid irradiation; HT, hypertension; RAS, renal artery stenosis; Pap. ca. thyroid, papillary carcinoma of the thyroid; CCF, congestive cardiac failure; EBV, Epstein-Barr virus; fem-pop, femoral popliteal

included, with 13 in each group. The parameters in the two groups were comparable (Table 2). Two patients within each group relapsed, but settled upon therapy with the other immunosuppressive. In all 4 of these patients, an accelerated ESR was a good marker of reactivation, having decreased with previous therapy and again with re-institution of therapy. A repeat Gallium scan post immunosuppressive therapy was negative in 11 of 12 patients. One patient interestingly still had a positive scan, and 8 months later reactivated.

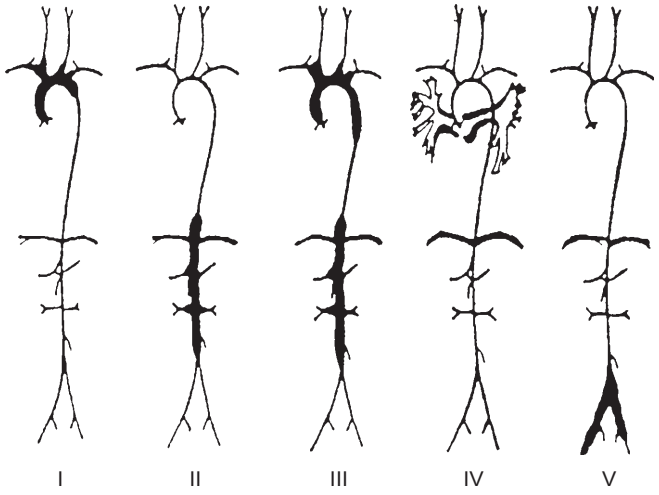

Fig. 2. Classification of Takayasu's arteritis. *Thicker areas* denote regions involved. Type IV indicates pulmonary arterial involvement. Type V disease includes iliac involvement alone or in combination with one of the other types. [Reproduced with permission from Pantanowitz D (1988) Modern surgery in Africa. Southern, Johannesburg]

Table 2. Additional immunosuppressive therapy – patients profiles*

	TLI (*n*=13)	Cyclo (*n*=13)
Systolic BP (mmHg)		
Pre treatment	158±10	144±9
Post treatment	119±8	126±8
C_{Cr} (ml/min per 1.73 m^2)[a]		
Pre treatment	104±35	94±30
Post treatment	108±38	100±33
Relapses	2	2
Alive	10	11
Deaths	3	2

C_{Cr}, Creatinine clearance
* There were no significant differences between the two groups
[a] C_{Cr} calculated by the Schwartz formula

Vascular surgery, usually to prevent further vascular compromise, was performed in 23 patients. Peri-operatively, heparin was usually used to prevent vascular occlusion, and low-dose aspirin was used in the long term for its antithromboxane effect. In total 33 procedures were performed (Table 3). The majority of autotransplants succeeded (11 of 15); the other modalities were unsuccessful (9 procedures).

Of our 31 patients, 7 have died. The angioplasty in 1 patient was performed prior to transfer to us and had already occluded. Two patients received no immunosuppressive therapy. One patient had bilateral aortorenal bypass grafts prior to transfer to our unit. Both grafts subsequently occluded, but renal function was salvaged with an autotransplant. The patient however succumbed as a result of a delayed aortoduodenal fistula related to the remaining goretex graft. The other patient died with severe hypertension and an intracranial bleed prior to surgical intervention.

Table 3. Surgical treatment of patients

Type of procedure	No. of procedure (*n*=33)
Unilateral autotransplants	9 (3 failed)
Bilateral autotransplants	6 (1 failed)
Nephrectomy	5
Coarctation repair	1
Bypass grafts (goretex)	4 (Bilaterally in 2 patients, all occluded)
Saphenous interposition	1
Axillo-femoral bypass	1 (failed)
Renal artery stent	2 (failed; re-stenosed, then successful autotransplant)
Angioplasty renal artery	1 (failed)
Cadaver transplants	4

Two patients who received cyclophosphamide died (1 had received only a 3-week course). In 2 other patients failure of autotransplants was due to occlusion. Three of the patients who received TLI died; 1 patient had severe pulmonary hypertension; 1 patient, who had no salvageable renal function, died 2 days after a cadaver transplant, secondary to a persistent aortic anastomotic bleed, as well as generalized oozing from the aorta; a third patient, who had had a nephrectomy and a failed autotransplant, also had TLI and a cadaver transplant, but died 20 months after the latter with a Epstein-Barr virus-induced hemophagocytic syndrome. On postmortem examination her aorta, which had been severely affected by Takayasu's arteritis prior to treatment, was normal macroscopically as well as microscopically. This reversal of significant pathology is remarkable, and stresses the potential of adequate immunosuppression.

Two further patients have received cadaver transplants, 1 of whom also had bilateral prosthetic grafts prior to transplant, but the prosthetic grafts occluded. She is doing well with good renal function, 9.5 years after her transplant. The other patient had bilateral autotransplants which occluded. She had also been given TLI prior to her transplant, but 7 years after treatment she presented with a papillary carcinoma of the thyroid. Treatment consisted of a radical thyroidectomy and radioablative iodine. It is important to stress that we have since had another TLI-treated patient (in preparation for transplantation) who did not have Takayasu's arteritis but also developed a papillary carcinoma of the thyroid 11 years after transplantation. In a further 14 patients who received TLI or cyclophosphamide, surgical intervention has been successful. Patients have been followed for a mean of 3.5 years (range 1–15 years). Three patients have been lost to follow-up (having been seen for 1, 3, and 3 years, respectively). One patient who had bilateral autotransplants had a normal term pregnancy, with a well baby delivered by caesarean section. Another patient is presently 22 weeks' pregnant.

Discussion

The mean age of our patients was 8.42 years, which is similar to other childhood reports [7, 10, 33]; 18 were female and 13 male, with a male:female ratio of 1:1.3. The disease usually has a greater female preponderance, although some authors have reported similar occurrences in the sexes [22, 34]. Our findings possibly reflect a dominant pre-pubertal ratio which is more even, as seen in other autoimmune diseases pre-pubertally. The disease also appears to have racial predilections [35]. This is reflected in our patient population, showing the majority to be black, with few Caucasians or patients of mixed race [7, 26]. However, there are far more black Africans in South Africa, and TB is more common.

The etiology of Takayasu's arteritis remains an enigma. An association with TB is suspected [8, 9, 36] and an autoimmune cause is also postulated [10]. Twenty-seven of our patients had strongly positive Mantoux tests, usually without active TB, suggesting an autoimmune trigger. It is important to emphasize that the black population without Takayasu's arteritis only have a 5% prevalence of strongly reactive Mantoux tests. Morrison et al. [9] demonstrated mycobacterial-like protein on the spindle-shaped cells of the aorta, using an anti-BCG antibody and immunoperoxidase techniques. In control patients this was negative. Using a monoclonal antibody, class II antigens were also found on the spindle cells [36]. The incidence of TB in South Africa currently ranges from 200/100,000 to a community in the Cape with 700/100,000 [37]. In our patients, 22% either had a history of being treated for TB or a strong family history.

Toma [35] reported a 70% positive tuberculin reaction, but failed to comment on this. An inflammatory cell infiltrate demonstrated histologically suggests a cell-mediated immune response. These infiltrating cells were previously shown to be CD8-positive lymphocytes [10]. However, as shown by Morrison et al. [9], class II antigens can be demonstrated, as confirmed by Seko et al. [38]. These authors also showed expression of the 65-kilodalton heat shock protein (HSP-65), class I antigens, and intercellular adhesion molecule-1 in aortic tissue of Takayasu's patients. The infiltrating cells, particularly γδ T-lymphocytes, a type of killer cell, may recognize HSP-65 and play a critical role in the vascular injury of Takayasu's arteritis by releasing perforin, a cytolytic factor. Immunohistochemical studies demonstrated that these cells were perforin-expression killer cells. Phenotypic studies revealed that 30% of cells consisted of γδ-lymphocytes. It has also been demonstrated that these cells release perforin onto the surface of arterial vascular walls [38]. These γδ T-cells have been implicated in the defense against *Mycobacterium tuberculosis* and may constitute the dominant cellular response to mycobacterial HSP-65 [39]. The possibility that there may be cross-reactants to heat shock protein and mycobacterial antigens does not detract from the accumulating evidence which suggests a cellular immunity-induced type of reaction. Without direct TB infection, but with reactions compatible with previous or present infection elsewhere, an autoimmune reaction is likely.

We hypothesized that mycobacterial TB would be a common trigger of Takayasu's arteritis in South Africa, because of the strong reaction (with ulceration common) to tuberculin in most of our patients. Atypical mycobacterial diseases would be less likely to give such a marked reaction, as would BCG itself. However, in Japan a strongly immunogenic BCG is given repeatedly if no reaction is obtained [40]. This could prime the patient to reacting abnormally, particularly if there was already an underlying immune disorder, albeit not necessarily severe. One of our Caucasian patients had the hyper IgE syndrome and had been given BCG on five separate occasions because of non-response. She had no history of evidence of previous TB, but presented at 11 years with diffuse Takayasu's arteritis, the hyper IgE syndrome having been diagnosed many years before, but after the BCG had been given repeatedly. She remained non-responsive to tuberculin testing. Hence, it would seem that a mycobacterial stimulus need not give a positive Mantoux in all patients, but could still be the prime trigger for Takayasu's arteritis.

The clinical features are protean and are classically divided into two phases, namely the early 'pre-pulseless' phase characterized by acute constitutional features and a late 'pulseless' phase manifested by vessel occlusion. Acute symptoms are usually of short duration, rarely lasting more than a few weeks, but may recur after intervals of weeks to years. These features are often unrecognized and manifestations of vascular occlusion or stenosis then dominate the clinical picture. Only 2 patients in our group had constitutional symptoms, 1 having been diagnosed with juvenile rheumatoid arthritis years previously on a basis of exclusion. Hypertension, secondary to renal artery stenosis and often associated with cardiac failure, was the most-common presenting feature in our patients (26 patients). This correlates with our angiographic findings of a predominance of abdominal aortic involvement with renal artery stenosis. Similar angiographic findings have been reported previously [33].

The diagnosis of Takayasu's arteritis, especially in the acute phase, remains difficult as a result of the heterogeneous clinical features. No specific or diagnostic laboratory investigation is available, and non-specific investigations may only indicate active inflammation. Angiography has been considered the investigation of choice in detecting the extent of vessel involvement in Takayasu's arteritis. Total aortography is usually mandatory in the initial evaluation of the disease [34, 35, 41]. The technique, however, is invasive and cumulative radiation toxicity with repeated studies to assess disease progression is a major risk. Newer imaging techniques, such as Doppler ultrasound and MRI, which are non-invasive and circumvent risks of radiation are increasingly reported [18]. Ultrasonography detects stenotic lesions of the carotid vessels with high sensitivity, is beneficial in monitoring patients with serial color flow Doppler studies, but is limited regarding which diseased vessels can be evaluated [42–44].

The performance of MRI in the diagnosis of Takayasu's arteritis is controversial. Yamada et al. [45] compared MRI with conventional angiography in 77 patients

with Takayasu's arteritis. In a further study, on a lesion-by-lesion basis, MRI was inferior to angiography in evaluating Takayasu's arteritis [46]. MRI may be useful in the follow-up of specific lesions or when radiation is contraindicated. However, it is expensive, requires expertise, and is not generally available in areas where the disease is most prevalent.

The management of Takayasu's arteritis remains complex, with no specific therapy available to date. We recommend a multifaceted approach comprising medical and surgical therapy. All our patients received antituberculous therapy. This remains a debatable issue, especially if no active TB is evident [7, 14, 23]. Most patients received low-dose aspirin for its anti-thromboxane effect. The use of corticosteroids in the active phase of the disease is widely accepted, but treatment regimens and therapeutic response are variable [47, 48]. Results are generally disappointing if treatment is not commenced in the early phase and irreversible vascular lesions have already developed. Most of our patients presented in this phase. Few studies indicate that the use of corticosteroids is sufficient in controlling disease activity, with the majority advocating the use of further cytotoxic therapy, including cyclophosphamide or methotrexate [18, 19, 21, 49].

TLI was used as an immunosuppressive to halt disease progression in Takayasu's arteritis [23], subsequent to its use in pre-transplant immunosuppression [28] and other autoimmune disease states [30]. We assessed 26 patients who received further immunosuppression in the form of TLI or cyclophosphamide. Profiles were comparable in the two groups (Table 2), as were the beneficial effects of both treatment modalities. However, the increased number of complications in our renal transplant patients prepared with TLI [50] would make cyclophosphamide a wiser first choice. We no longer use TLI in Takayasu's arteritis because of further complications listed below.

Besides medical therapy, surgical intervention is frequently required to alleviate end organ ischemia resulting from vascular damage. Many strategies are recommended, ranging from percutaneous transluminal renal angioplasty (PTRA) to bypass grafting and autotransplantation. Successful cases are increasingly reported with PTRA [30, 51, 52], but restenoses and repeat angioplasty remain risk factors.

We have strongly advocated the use of autotransplantation, particularly in the quiescent phase of the disease, having had higher failure rates with other modalities. (In 2 patients goretex grafting clotted, 1 stent failed, the other stent re-stenosed, and with PTRA a thrombus occurred.) Peri-operatively, we have generally used heparin in the short term. In contemplating autotransplantation we have recommended the classification of Takayasu's arteritis described in Fig. 2, since evaluation of the aoto-iliac vessels is obviously necessary [25, 53]. Iliac vessel involvement has not been used in the new classification of angiographic findings in Takayasu's arteritis based on the Takayasu Conference in 1994 [54]. Failed autotransplants in our series occurred in children 5 years and younger. The majority of our surgery was performed by a single surgeon, and improved outcome in subsequent cases may be due to accumulated experience [24].

In his prospective studies on the natural history of Takayasu's arteritis, Ishikawa [15] estimated a 5-year survival of 83% in all patients with Takayasu's arteritis and a 10-year survival of 58% in patients with severe disease. There are few follow-up studies in children, and the mortality rate has ranged from 21% to 40% in the short term [6, 7, 27]. In our patients who died, the major causes were uncontrolled hypertension or complications related to surgery. With the follow-up of up to 15 years, our mortality has been 22%. Compared with goretex grafts, our morbidity has decreased with autotransplantation [23].

Thus far no untoward effects of immunosuppression or the disease itself on fertility have been noted in our patients. One patient who had received TLI and had bilateral autotransplants recently delivered a full-term normal baby. ACE inhibitors with teratogenic effects, such as scalp defects and renal failure in the fetus, are contraindicated in pregnancy [55]. This patient was unfortunately exposed to ACE inhibitors, having returned for a follow-up visit when she was already 24 weeks' pregnant. Fortunately the baby suffered no complications. We postulate that the vasodilatory properties of calcium channel blockers may have had a protective effect. Another patient is 22 weeks' pregnant and the ACE inhibitor has been withdrawn. The inflammatory activity of the disease is not usually exacerbated by pregnancy. Markers of poor maternal and fetal outcome include hypertension, extensive or aneurysmal disease, and cardiac failure. A multidisciplinary approach including obstetricians and physicians is required [56, 57].

One of our patients was recently diagnosed with papillary carcinoma of the thyroid. She had received TLI and had a cadaver transplant. It is very likely that her malignancy is related to her low-dose irradiation [58, 59]. This is supported by the observation of a second papillary carcinoma of the thyroid in another patient who underwent TLI prior to renal transplantation. This gives a prevalence of 1 in 25, compared with a maximal described prevalence of 1 in 10,000, but in this age group the prevalence would be unlikely to be more than 1 in 100,000 [60]. Because of this, we no longer advocate the use of TLI in Takayasu's arteritis nor in renal transplantation.

In conclusion, Takayasu's arteritis remains an ongoing challenge, diagnostically and therapeutically. The etiology remains obscure, with an autoimmune pathogenesis postulated. TB seems to be a common trigger in our experience. Early diagnosis and therapy, possibly aided by the newer imging techniques, is essential for a good prognosis. The chronicity and relapsing nature of the disease require treatment regimens of low toxicity. A combination of these modalities and surgical intervention may improve the outcome.

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Literature abstract

J Am Soc Nephrol (1997) 8:1546–1552

Association between vitamin D receptor gene polymorphism and relative hypoparathyroidism in patients with chronic renal failure

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To study the influence of vitamin D receptor (VDR) gene polymorphism on parathyroid cell function in chronic renal failure, 85 patients who had serum PTH levels <12 pmol/L (the low intact PTH [iPTH] group) and 46 patients who had serum iPTH levels >60 pmol/L (the high iPTH group) were selected out of a total dialysis population of 170 individuals. As a result of subequent exclusions based on several criteria in both groups (diabetic patients, serum aluminum levels, serum calcium levels, and time on dialysis), the final low iPTH group consisted of 34 patients and the final high iPTH included 32 patients. A healthy control population (*n*=120) and 162 of the 170-patient dialysis population served as control group. VDR gene polymorphism was determined by digestion with the BsmI enzyme and single-strand conformation polymorphism analysis of PCR amplified fragments. Serum iPTH levels were lower in patients with the BB genotype than in those with the Bb or bb genotype, both in the total dialysis population and when the various exclusion criteria were applied. No differences in genotypic and allelic frequencies were found between the healthy control population and the high iPTH group. However, the genotypic distribution was significantly different in the low iPTH group of patients before and after applying all exclusion criteria (*P*=0.037 and *P*=0.018, respectively). In the final selected population, the bb genotype was less frequent in the low iPTH group than in the total dialysis population (14.7% versus 36.4%; odds ratio, 0.3; confidence interval, 0.11 to 0.82; *P*=0.01). Conversely, the BE genotype was over-represented in the low iPTH group (23.3% versus 19.7%; odds ratio, 1.9; confidence interval 0.85 to 4.3; *P*=0.1). In addition, the bb genotype and the b allele frequencies were lower in the low iPTH group than in the high iPTH group (14.7% versus 34.4%, *P*=0.06, and 41.2% versus 60.9%, *P*=0.02, respectively), and the BE genotype and the B allele were significantly more frequent in the low PTH group than in the high iPTH group (32.3% versus 12.5%, *P*=0.05, and 58.8% versus 39.1%, *P*=0.02, respectively). Thus, VDR gene polymorphism influences parathyroid function in chronic renal failure.