EXTENDED REPORT

Magnetic resonance imaging in the diagnosis and follow up of Takayasu's arteritis in children

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Background: Takayasu's arteritis (TA) has a mortality rate of up to 40% in children. Because the clinical presentation of TA is often non-specific, accurate and prompt diagnosis depends on a high degree of awareness and appropriate laboratory and imaging studies.

Objective: To examine the use of advanced magnetic resonance imaging (MRI) in evaluating, gauging activity, and following the complications of TA.

Methods and results: T₁ weighted, T₂ weighted, contrast enhanced MR images, and MR angiograms of the chest and abdomen were obtained in three children (age range 11–14 years). The MRI studies confirmed the diagnosis of active TA and were repeated to evaluate response to treatment. Two patients showed complete resolution of lesions found on MRI at six and 12 months' follow up, while the third patient showed no significant improvement.

Conclusion: MRI can be used to help establish the initial diagnosis of TA in children, and it can also be used to monitor disease activity and to guide treatment.

Takayasu's arteritis (TA) is a chronic inflammatory disease that affects the aorta, its main branches, and the pulmonary arteries. The disease has been associated with streptococcal infections, rheumatic fever, tuberculosis, rheumatoid arthritis, and other immune mediated conditions.¹

Angiography has been the best method of establishing the diagnosis of TA and in identifying complications such as arterial stenoses, aneurysms, and collateral shunting. Early in the disease, smoothly thickened vessel walls, which may be the only manifestation of vascular inflammation, may not be detected by conventional angiography.² In the past decade, advanced tomographic imaging techniques, such as ultrasonography,³ computed tomography (CT), CT angiography,^{4,5} and most recently, magnetic resonance imaging (MRI),^{6–8} have shown promise in the diagnosis of TA. These tomographic techniques can visualise the thickened vessel wall directly. MRI, in addition, can show other signs of active inflammation such as mural oedema with T₂ weighted imaging and increased wall vascularity with contrast enhanced imaging.^{9,10} Therefore, MRI can help to monitor disease progression non-invasively and help to guide treatment. MRI also has the added benefit of not subjecting children to ionising radiation, thus permitting repeated studies for follow up. In this report, we describe the cases of three children in whom MRI helped to establish the initial diagnosis of TA and helped to monitor their response to treatment.

CASE SERIES

PATIENT 1

Initial evaluation

Patient No 1 is a 14 year old white boy with one year history of fevers, weight loss, leg cramps, and easy fatigability. One day before admission, he presented to another hospital with dizziness and orthostatic hypotension. When a fall in packed cell volume was found, aortic dissection was considered, and he was referred to our institution. On examination, he had a reversed arm-leg systolic blood pressure discrepancy of 50 mm Hg and the radial pulses were diminished compared with the femoral pulses. Auscultation disclosed a diastolic murmur and bruits over the carotid, brachial, and femoral arteries. Laboratory tests showed an abnormal haemoglobin (108 g/l), erythro-

cyte sedimentation rate (ESR) (60 mm/1st h), and C reactive protein level (4 mg/ml). His renal function and serologies were normal. An MRI study was performed. T₁ weighted images showed markedly and diffusely thickened aortic wall involving the ascending aorta, the aortic arch and its branches, and the abdominal aorta at the level of the renal arteries (fig 1A). The ascending aorta and aortic root were significantly dilated at 41 mm as compared with normal angiographic data compiled by Aluquin and colleagues (95th centile for body surface area is 26 mm)¹¹ (fig 1A). The abnormal segments of the aorta demonstrated increased T₂ weighted signal intensity and gadolinium contrast enhancement (fig 2A). Contrast enhanced MR angiography showed irregular luminal wall of both carotid and subclavian arteries (web extra figure W1). Moderate valvar regurgitation was found on cine MR imaging (web fig W2). Mild renal artery narrowing was also noted. The pulmonary and coronary arteries appeared normal.

Follow up

Treatment was started with intravenous methylprednisolone (3 mg/kg/day) and oral cyclophosphamide (60 mg/day) together with multiple antihypertensive drugs. He improved clinically and his ESR normalised to 1 mm/1st h. He was discharged after two weeks while prednisone was slowly tapered and monthly intravenous cyclophosphamide was received. Repeat MRI studies one, three, and six months later showed no changes in wall thickening and a slight increase in dilatation of the ascending aorta to 45 mm. One year later, a repeat MRI showed marked improvement in wall thickness of the aorta, carotid, subclavian, and axillary arteries (fig 1B). It also showed decreased T₂ weighted signal intensity and gadolinium contrast enhancement (fig 2B). Serial echocardiograms showed stable left ventricular dimensions, stable ascending aorta diameter, and decreased aortic regurgitation. Cyclophosphamide was discontinued and treatment was started with weekly low dose methotrexate.

Abbreviations: CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; TA, Takayasu's arteritis

Figure 1 (Patient 1) (A) T_1 weighted axial images showing a dilated ascending aorta (long thin arrow) and significant wall thickening of the descending aorta (short thick arrow). (B) Improvement in wall thickness after 12 months of treatment.

Patient 2

Initial evaluation

Patient No 2 is a 13 year old white girl who had had leg cramps, headaches, and angina for five years. She was found to be hypertensive for three years and was diagnosed with aortic coarctation. On examination, four arm blood pressure measurements showed no significant gradient and a systolic murmur was heard along the right upper sternal border. Serial echocardiograms suggested an increasing pressure gradient across the coarctation, and she underwent cardiac catheterisation for possible balloon angioplasty and stenting. On angiography, we found stenoses of the proximal right subclavian, left common carotid and left subclavian arteries in addition to the discrete aortic coarctation. Laboratory investigation showed a raised ESR (48 mm/1st h). MRI was then performed to evaluate the wall thickening of the major arteries. T_1 weighted images disclosed marked thickening of the ascending aorta, extending into the origins of the cervical great vessels, particularly the brachiocephalic artery (web fig W3A). These vessels showed increased T_2 weighted signal intensity and contrast enhancement (web fig W4A). MR angiography showed focal narrowing at the aortic isthmus and at the origin of the left subclavian artery (web fig W3B). The left vertebral artery had a small calibre with segments of irregularity in the proximal and mid-portions.

Follow up

Treatment was started with weekly subcutaneous low dose methotrexate (25 mg) and oral prednisone (1 mg/kg/day). Her ESR continued to be raised at 27 mm/1st h six months later and she continued to have fatigue and leg cramping. A follow up MRI at that time showed no interval change in the vessel wall thickening but decreased enhancement of the aortic wall (web fig W4B). Her regimen was then changed to cyclophosphamide.

Her fatigue and leg cramping resolved after two to three months of cyclophosphamide treatment.

Patient 3

Initial evaluation

Patient No 3 is an 11 year old Asian girl who suddenly developed iritis and uveitis unresponsive to ophthalmic antibiotics. On examination, she was found to be hypertensive, tachycardic, and had conjunctival injection. Laboratory tests showed a raised ESR (71 mm/1st h), and a positive purified protein derivative test (20 mm induration). Serological tests and catecholamine levels were normal. Gastric acid-fast bacillus aspirates and cultures were negative. A chest radiograph showed a prominent aortic arch with an undulating contour of the descending aorta suggestive of coarctation. Imaging of the chest showed multiple small pulmonary nodules and mediastinal lymphadenopathy. Axial T_1 weighted MR images demonstrated abnormal wall thickening of the mid-descending aorta at the level of the left atrium extending to the level just superior to the origin of the coeliac trunk (web fig W5A). The abnormal segment showed increased T_2 weighted signal intensity (fig 3A) and gadolinium contrast enhancement. Contrast enhanced MR angiography also showed irregularity in the contour of the left lateral margins of the descending aorta. A diagnosis of TA and primary tuberculosis was made.

Follow up

Treatment was started with prednisone (2 mg/kg/day), isradipine, atenolol, and a triple drug regimen for tuberculosis. She improved clinically after two weeks and her prednisone and antihypertensive drugs were tapered gradually over seven months. A repeat MRI showed interval resolution of the mediastinal lymphadenopathy and pulmonary nodules. Wall thickness, T_2 weighted signal intensity (fig 3B and web fig W5A),

Figure 2 (Patient 1) (A) Gadolinium contrast enhancement of the abdominal aortic wall (arrows). (B) Resolution of wall enhancement after treatment.

Figure 3 (Patient 3) (A) Increased signal intensity of the descending aortic wall (arrow) on T₂ weighted axial images. (B) Resolution of inflammation after treatment.

and contrast enhancement of the distal thoracic aorta were significantly reduced.

DISCUSSION

TA is a chronic inflammatory disease of unknown cause characterised by granulomatous vasculitis of medium and large arteries, principally the aorta, its main branches and the pulmonary arteries. It has protean manifestations ranging from asymptomatic patients with incidental findings of unequal pulses and limb blood pressures, bruits, or hypertension to dramatic presentations in the form of congestive heart failure, cerebrovascular accident, ruptured aortic aneurysm, or blindness.^{1,12} TA classically exhibits a triphasic pattern of expression consisting of a systemic non-vascular phase, a vascular inflammatory phase, and a quiescent, “burnt out” phase.¹³ However, this classic presentation holds true only in a minority of patients because both inflammatory and fibrotic changes may coexist at one time owing to the chronic and recurrent nature of TA.^{1,14}

TA is associated with mycobacterial infections, especially in children. A study by Morales *et al* of 26 children with TA found a remarkable prevalence of positive purified protein derivative of 73% compared with the 22% reported in healthy school children.¹⁵ Jain and colleagues in their study of 24 patients with TA showed an incidence of 29%.¹⁶ In adults, one necropsy study reported a 70% prevalence of caseating granulomatous lymphadenitis compared with 8% of the control population.¹⁷ Whether this association reflects an immunopathogenic mechanism in the development of TA or merely an epiphenomenon (given the endemicity of tuberculosis in certain regions) is not known.

TA has been rarely recognised in children,¹⁵ as systemic features predominate and lead to misdiagnosis as systemic lupus erythematosus or juvenile rheumatoid arthritis. In one series, the higher ESR and presence of systemic features aided in the correct diagnosis, but in a separate report a delay in the diagnosis in children compared with adults (19 versus five months) was found.^{18,19} TA in children tends to have a more aggressive course. Two series have shown a mortality rate of 35–40% by five years.^{15,20} Thus, it is imperative to have a high degree of awareness and low threshold for diagnostic evaluations.

The diagnosis of TA is based on characteristic findings of the diseased aorta and its major branches seen on angiography. This is demonstrated by luminal abnormalities such as stenosis or aneurysmal dilatation of the aorta, its major branches, and the pulmonary arteries.¹² In the acute/early phase of the disease the pathological findings depict florid inflammation in the tunica media and tunica adventitia, thus giving rise to

reactive thickening of the intima.²¹ Angiography can evaluate the luminal calibre of the aorta but not the inflammation or thickening of the vessel wall,⁹ and thus, early systemic disease can be missed. Matsunaga *et al* illustrated this point when they noted the difficulty in assessing thickness of the pulmonary arterial wall with angiography.⁶ In our second patient, the initial MR imaging showed extensive involvement of the ascending aorta, which was not detected on angiography. Furthermore, recent reports showed that angiography is associated with a high rate of ischaemic complications thought to be related to the increased blood coagulability in these patients.^{22,23} Significant radiation exposure and the inherent risk of invasive arterial angiography preclude serial follow up studies. A non-invasive technique without radiation exposure, such as MRI, would be greatly desirable.

The versatility and safety of MRI make it an ideal imaging modality for TA. Like conventional angiography, MR angiography can depict luminal stenoses, dilatation, aneurysm, contour irregularities, and dissection.⁸ The multiplanar capability of MRI also permits a clear assessment of the extent of the aortic lesions in a longitudinal plane. During the active phase of the disease, T₁ weighted images typically show thickened arterial walls. T₂ weighted images may show increased mural signal intensity, reflecting tissue oedema,⁹ and contrast enhancement of vessel walls suggests increased vascularity in chronic active lesions.¹⁰ Cardiac cine imaging may depict aortic regurgitation, which is important because heart failure has replaced cerebrovascular accident as the most life threatening complication of TA.²² Similarly, MRI provides excellent visualisation of the pulmonary arterial wall. Yamada and colleagues showed that the pulmonary arterial abnormalities, which were seen in 70% of their cohort, were specific to TA and were not seen in cases of atherosclerosis or other arteritides.²⁴ To date though, there has been no direct comparison of conventional angiography and MR imaging on large vessel vasculitis.

Early detection and treatment of TA related lesions may prevent development of irreversible fibrosis and vascular stenosis. In addition, during the follow up period, constitutional symptoms and inflammatory parameters do not necessarily parallel the activity of the disease.¹⁴ MRI may serve as a surrogate marker for disease activity, permitting better management decisions.

In this study we have shown that the MRI findings correlate with clinical and serological parameters and parallel improvement of these during follow up. In the first patient, however, the findings of mural oedema improved only after one year of treatment despite a rapid clinical response. We suggest that structural abnormalities may lag behind systemic clinical improvement and should be carefully monitored with follow up imaging. Apart from revealing the persistence of mural

thickening, the follow up MR imaging on patient No 2 allowed us to determine a decrease in contrast enhancement. This additional finding, which can translate to reduced vascularity, may reflect progression to scar tissue.

No prospective studies have been performed to date on the sensitivity of MRI compared with serological markers. Possibly, MRI is no more sensitive than the latter. However, MR imaging is more specific because we can identify the abnormality specifically to larger vessels. As illustrated earlier, MRI has the advantage of seeing the extent of the disease for follow up as well as identifying the regions at risk for fibrosis and stenosis.

We have reported three cases of TA in children who had a wide range of disease manifestations, and their corresponding MRI findings. We were also able to monitor disease activity. Our results are consistent with published reports on older patients. Although there were no complications in any of our studies, the limitation of MR imaging in young children is the requirement of some sedation and its high cost. Assessment of the true accuracy and use of MRI in the initial evaluation and follow up of patients with TA awaits a comprehensive prospective clinical trial.

Additional figures can be found on the website at www.annrheumdis.com

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