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An Alternative Approach of Managing Acute Rheumatic Fever

Patel AN[1], **Hawley DP**[2] **and Rangaraj S**[1*]

[1]*Department of Dermatology and Paediatric Rheumatology, Nottingham Children's Hospital NHS Trust, Nottingham, NG7 2UH, UK*

[2]*Department of Paediatric Rheumatology, Sheffield Children's NHS Foundation Trust, Western Bank, Sheffield, S10 2TH, UK*

[*]**Corresponding author:** Satyapal Rangaraj, Consultant in Adolescent and Paediatric Rheumatology, Department of Dermatology and Paediatric Rheumatology, Nottingham Children's Hospital NHS Trust, Nottingham, NG7 2UH, UK, Tel: 01159 249924; E-mail:satyapal.rangaraj@nuh.nhs.uk

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Abstract

Acute rheumatic fever is prevalent across the world and carries a high mortality and morbidity predominantly due to its complication of carditis. The underlying pathogenesis involves a complex interaction between the infective agent and the immune system. Traditionally, management has focused on preventing recurrent infections by prophylactic antibiotics. We illustrate two cases managed with immunosuppression which can be a valuable additional tool in managing this global health problem.

Keywords: Acute rheumatic fever; Rheumatic Heart Disease; Methotrexate; Streptococcal infection

Background

Acute Rheumatic Fever (ARF) is an auto-immune consequence of infection with the bacterium Group A streptococcus (GAS), characterized by a sub-acute generalized inflammatory response particularly affecting the heart, joints, brain and skin. The significance of rheumatic fever is almost solely due to its cardiac sequel. Cardiac involvement leads to Rheumatic Heart Disease (RHD). People who have had ARF previously are at higher risk of subsequent episodes [1] associated with further cardiac valve damage. RHD is the most common form of paediatric heart disease in the world and is the leading cause of cardiac death in the first five decades of life [2]. Worldwide, it is estimated that there are 20 million cases of RHD, and up to 500,000 patients die from this disease each year [3,4].

Incidence of >10/100,000 is reported in Eastern Europe, Middle East, Asia and Australasia. Incidence of ≤ 10/100,000 was found in Western Europe and America [5]. This difference is often attributed to improved hygiene standards [6,7].

In attempting to prevent RHD, efforts thus far have focussed largely on prevention of recurrent streptococcal infections in the form of primary or secondary prophylaxis with Penicillin V or Erythromycin [8-11], and controlling the inflammatory process with aspirin and steroids [12].

The diagnosis of ARF is established largely on clinical grounds. The initial description of the clinical manifestations, now known as the "Jones criteria", was published by Jones in 1944 and revised most recently in 1992 [13,14]. The major criteria include carditis, polyarthritis, chorea, erythema marginatum and subcutaneous nodules. The minor criteria include arthralgia (counted only when arthritis is not present), fever, elevated acute phase reactants and an electrocardiogram showing a prolonged PR interval. If supported by evidence of a preceding GAS infection, the presence of two major manifestations or of one major and two minor manifestations is indicative of a high probability of ARF.

There is ongoing debate if post streptococcal reactive arthritis (PSRA) is a different entity to ARF, or if it is part of the same spectrum. PSRA is a term coined in 1980's to differentiate a group of patients similar to those with ARF but with no/less incidence of carditis and where modified Jones criteria is usually not met.

PSRA patients are generally older, have a longer interval between GAS infection and symptom onset, and respond less dramatically to salicylates than ARF patients. The course of PSRA is characterized by arthritis that, in contrast to ARF, is additive, non-migratory and is frequently chronic [15-18]. Extra-articular manifestations including renal involvement can be present. Factors of the host, the Streptococcus and the immune response involved in the development of PSRA are scarcely explored, hampering comparisons with ARF. As prevalence of ARF decreases in United States and Western Europe, PSRA is coined more frequently; however, a diagnosis of ARF trumps that of PSRA. Treatment of PSRA is variable in comparison to ARF, with most treatment being concentrated on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and short/ long term antibiotics [15,16]. Here we illustrate management of two children, who meet the modified Jones criteria for ARF.

Case 1

A twelve year-old girl presented with a two week history of myalgia and general malaise. Seven days later she gave a history of an evanescent rash that started on the thighs and progressed to the face and trunk accompanied by a swinging pyrexia of up to 40 degrees centigrade. Four days prior to presentation she had developed a sore throat and joint pains affecting the left ankle and wrist. She was unable to weight bear. Initial investigations yielded raised acute inflammatory markers (C-Reactive Protein 350 mg/L, White Cell Count 20.5×10^9/L , Neutrophils 17.7×10^9/L Antistreptolysin O Titre 400 units/ml and Erythrocyte Sedimentation Rate 107 mm/hr). A urine dipstick on admission showed a 1+ of blood and protein. The following day intravenous antibiotics were commenced in the form of cefotaxime and benzylpenicillin with teicoplanin added two days later. Intravenous fluids were also commenced for the septic picture. Despite all these interventions the patient remained pyrexial. Abdominal pain was becoming a significant complaint. An abdominal ultrasound was

performed and was normal. Repeated blood and urine cultures remained negative. Viral serology was negative. Her Anti-Nuclear Antibody (ANA) titres were normal; rheumatoid factor was not done. The patient was tachycardic and tachypnoeic and so a chest X-ray and echocardiogram were performed showing a pericardial effusion, a pericardial thrombus and bilateral pleural effusions. Inflammatory markers remained elevated and the overall impression was that of a post-infectious inflammatory response. There was restricted movement of the left knee and hip; an ultrasound scan showed no effusion. The white cell count (29.6×10^9/L), neutrophils (25.9×10^9/L) and platelets (546×10^9/L) continued to rise. Her serum Ferritin was elevated at 1112 micrograms/L. Muscle enzymes were normal. It was decided to administer treatment with three consecutive once-daily pulses of intravenous methyl-prednisolone (30 mg/kg). This gave an excellent response within two days. However two days later, symptoms of high grade fever, tachycardia and tachypnoea returned accompanied by a widespread rash. She warranted admission into paediatric intensive care and symptoms persisted despite oral prednisolone and further pulses of intravenous methyl-prednisolone. Weight loss and worsening polyarticular arthritis set in. A repeat chest X-ray showed cardiomegaly with globular configuration. Some linear interstitial densities centrally and bilateral pleural effusions were seen. The cardiac enlargement and pleural effusions were associated with atelectasis in the underlying lung, particularly at the bases. Bilateral pleural drains were inserted as well as a pericardial drain. Cultures were sent again but remained negative. This intervention of drain insertion alleviated symptoms. Core body temperature continued to spike accompanied by arthralgia; antibiotics were of no help. Immunosuppression with oral prednisolone and occasional pulses of methylprednisolone (three in total) remained the only intervention to alleviate symptoms. A diagnosis of ARF was achieved as the Jones diagnostic criteria had been met (polyarthritis, pericarditis, fever, elevated acute phase reactants).

The need for longer term immunosuppression had arisen and thus methotrexate was commenced and increased steadily, reaching a dose of 20 mg per week sub-cutaneously. Over four to six months her symptoms came under control. Her inflammatory markers, including serum Ferritin, returned to normal and remain low. She remains in remission, participating in all routine activities as before onset of her illness, for more than three years since her initial presentation with complete resolution of her carditis.

Case 2

The second case involved an eight year-old girl with a five week history of intermittent rash, high temperatures, poor appetite, malaise and painful joints. Examination showed an urticarial rash over chest and arms, active precardium with high temperature of 39.5 Celsius, with rest of systemic examination being normal. Investigations showed a raised neutrophil count (24.4×10^9/L), platelet count (542×10^9/L), CRP (68 mg/L), ESR (54 mm/hr), Antistreptolysin O Titre (800 units/ml) and CK (828 U/L). Blood cultures and throat swabs did not show any growth. Chest X-ray, urine dip, and echocardiogram were all normal. Viral serology yielded no significant results. ANA was negative. Initial antibiotics in the form of benzylpenicillin were commenced intravenously. This proved to be of no benefit. An oncology opinion was sought. A bone marrow trephine was performed as part of examination which was normal. Neuroblastoma screen was undertaken which was normal. An underlying malignancy was ruled out. She was managed with high dose NSAIDs. Over the next four weeks, symptoms persisted with intermittent high temperatures; her inflammatory markers continued to rise with ESR at 120 mm/hr and Platelets at 686×10^9/L. Three doses of intravenous methylprednisolone pulse were administered and she was clinically better for 2-3 weeks during which time she was discharged home. However, she developed swelling and restrictions in multiple joints after this period. A diagnosis of ARF was reached due to meeting the diagnostic criteria for the disease (polyarthritis, fever, raised acute phase reactants). Oral steroids were commenced at a dose of 30 mgs/day for a week and tapered down by 10 mgs every week to a maintenance dose of 10 mgs. Her tiredness, temperatures and joint swelling remained under reasonable control on steroids but she was flaring on every attempt at further reduction of steroid dosage. As she remained steroid dependant after 3 months, subcutaneous methotrexate at a dose of 20 mgs a week was commenced predominantly to control her joint symptoms. Two further 3 day pulses of intravenous steroids were necessary to control her polyarthritis, temperatures and tiredness until methotrexate became effective over a period of 3 to 4 months. Her symptoms fully settled and she was weaned off oral steroids in 6 months after commencing methotrexate. Her flares were non-existent on regular treatment, her inflammatory markers were normal and she was able to attend school full time. Since achieving remission she had continued to remain so for over 2 years.

Discussion

ARF is a result of interplay between a susceptible host, virulence of GAS strain and environmental features [19,20]. For over a hundred years, genetic predisposition to rheumatic fever has been explored [21]. Recently, studies have shown both MHC-related and non-MHC related genetic associations in ARF [21-26]. Virulence of GAS is based on differing constituents of GAS including the cell wall, capsule and M-proteins among others as well as specific serotypes [27-31]. ARF is well known to affect the underprivileged group in difficult socio-economic conditions, with poor nutrition, access to healthcare and sanitation facilities.

The pathogenic mechanisms are poorly understood but involve a highly complex interaction between the specific virulence factors and immune system. The immune response is similar to autoimmunity, with both humoral and cellular immune reactions being activated [32]. CD4 cells are predominantly present in the acute stage of carditis [33] and this cellular response is implicated in chronic valvular lesions. The subsequent damage following ARF is due to inflammation resulting from an elevated and inappropriate immune response state. While the focus in preventing RHD has predominantly been on preventing infection, there has been little attention on controlling the inflammatory responses which is the main driving force. As the case series above demonstrates, we were able to achieve and maintain remission by solely using immunosuppressive agent rather than use any antibiotic prophylaxis; an alternative approach may be equally or more effective in dealing with this enormous health burden.

Low dose methotrexate is known to be safe and is being used more commonly [34,35]. The frequency of use at once weekly may ensure better compliance. Further large studies exploring route, dose, frequency and duration are necessary.

Conclusion

Immunosuppression may be a valuable additional tool to secondary antibiotic prophylaxis in preventing complications from ARF. Further elaborate studies are necessary to prove its efficacy and value. This case

series helps to provide an alternative view on approach to managing the prevalent problem of ARF and RHD.

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