CASE REPORT

Failure of oral penicillin as secondary prophylaxis for rheumatic heart disease: a lesson from a low-prevalence rheumatic fever region

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Accepted 15 October 2015

SUMMARY

Our patient is an 18-year-old Caucasian woman from the UK who developed severe mitral stenosis on a history of childhood acute rheumatic fever (ARF) and rheumatic heart disease (RHD). She had been reporting of her oral penicillin secondary prophylaxis regimen since diagnosis. At the age of 15 years, a new murmur was discovered during routine cardiac follow-up. An echocardiogram confirmed moderate-severe mitral stenosis. One year later, her exercise tolerance significantly deteriorated and she subsequently underwent balloon valvuloplasty of her mitral valve to good effect. Our case emphasises the evidence base supporting the use of monthly intramuscular penicillin injection to prevent ARF recurrence and RHD progression; it also emphasises the reduced efficacy of oral penicillin prophylaxis in this context. It particularly resonates with regions of low rheumatic fever endemicity. The long-term cardiac sequelae of ARF can be devastating; prescribing the most effective secondary prophylaxis regimen is essential.

BACKGROUND

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are now fortunately rare in the UK and most parts of developed countries, but remain a significant health threat in developing countries and in some indigenous regions of wealthier countries. Much of the current research into the management and prevention of ARF originates from, and is focused on, these countries. However, clinicians in low-risk populations for ARF need to remain informed about this disease: many of these countries have increasingly diverse populations, with immigrant populations from high-prevalence rheumatic fever (RF) regions.

ARF results from an improper immune response to infection with group A *Streptococcus* (GAS) in a susceptible individual.^{1 2} It is most common just before adolescence and is rare in the very young or in adults over the age of 35 years.^{1 2} Patients who have had ARF are at an increased risk of recurrence, greatest in the first 5 years after diagnosis.^{1 3} Recurrences may be clinically silent.⁴ RHD can result from the first RF attack but more usually represents years of cumulative damage to valves from recurrent acute ARF attacks.^{5 6} Therefore, while the incidence of ARF is highest in childhood, the incidence of RHD peaks in adulthood.^{1 2 5}

The natural history of RF was markedly altered by the introduction of penicillin in the

1940s–1960s.^{7 8} Secondary penicillin prophylaxis prevents reinfection with GAS and therefore helps protect against ARF recurrences and the development or deterioration of RHD. Indeed, in the absence of recurrence, rheumatic carditis can naturally improve over several years.^{9 10}

Selection of the most effective secondary prophylaxis regimen for these patients is paramount. In earlier decades, it was established by careful observation in the UK and the USA that intramuscular penicillin was superior to oral antibiotic regimens;^{8 11 12} this has been confirmed by meta-analysis of all treatment RCTs.¹³ However, oral penicillin prophylaxis regimens are still used in some centres: clinicians in low-incidence countries paradoxically may not have the health community supports to aid long-term intramuscular penicillin administration; RF management guidelines may not be well established in these areas.

CASE PRESENTATION

Previously, a 7-year-old Caucasian girl presented with Sydenham's chorea in the UK. This, along with a new cardiac murmur and a significantly raised antistreptolysin O titres (>800 units/mL), promptly led to a diagnosis of ARF. There was no family history of streptococcal infections; there was no social or travel history of note. The only clinical signs of carditis at this time were the new systolic murmur and an echocardiogram confirming mild mitral and aortic regurgitation through morphologically normal valves. Her ECG remained normal and there was no obvious rub on examination. She was treated with aspirin, penicillin and valproate and a steady improvement in her chorea was noted over 5 months. She was started on a twice daily oral penicillin secondary prophylaxis regimen to which she remained fully compliant from initial diagnosis up until the present time.

The patient remained under cardiological and neurological paediatric review. Cardiovascular examination remained normal; periodic echocardiograms confirmed the presence of trivial/mild mitral and trivial aortic regurgitation only. She developed no other health issues and, aside from her oral penicillin prophylaxis, she took no regular medications.

At age 15 years, by then under the care of adult specialist services, an echocardiogram was arranged following the discovery of a new murmur and a tapping apex beat. This showed moderate-to-severe mitral stenosis with features of RHD. At this point,

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To cite: McGlacken-Byrne SM, Parry HM, Currie PF, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212861

she remained symptom free and was initially followed up with serial echocardiography and exercise testing.

INVESTIGATIONS

One year later, in 2012, her exercise tolerance significantly deteriorated. A repeat echocardiogram at this time estimated the valve area at 0.9 cm^2 by planimetry and 1.1 cm^2 by pressure half-time method. Peak forward velocity was 2.45 m/s . The left atrial diameter (M-mode) was 4.4 cm in the long-axis view and 4.9 cm in the apical views, with an area of 23 cm^2 . There was no tricuspid regurgitation and the right ventricular volumes and function were normal.

Exercise testing confirmed a marked deterioration in exercise tolerance: she managed 10.5 min of the Bruce protocol in early 2011, dropping to 6.5 min in September 2012 with the patient reporting increasing fatigue and dyspnoea. She remained in sinus rhythm.

TREATMENT

She was referred for mitral balloon valvuloplasty which was performed in December 2012. Transoesophageal echocardiography guidance confirmed severe mitral stenosis without visible calcification and only very mild mitral regurgitation. There was marked fibrosis of the subvalvular apparatus. The valve was dilated by balloon inflation to a maximum diameter of 27 mm . The mean gradient fell from 15 to 6 mm Hg with only mild associated regurgitation.

Exercise tolerance significantly improved following the procedure and the patient managed 10 min of the Bruce protocol on further testing 8 months later. She was not anti-coagulated as she remained in sinus rhythm. Prophylactic oral penicillin was continued.

OUTCOME AND FOLLOW-UP

Recent echocardiography showed a mitral valve area 1.5 cm^2 by planimetry and 1.8 cm^2 by pressure half-time method with a left atrial diameter of 3.7 cm and only mild mitral regurgitation. She is once again entirely asymptomatic from a cardiac point of view and is under annual review. She remains reporting of her secondary prophylaxis.

DISCUSSION

Multiple studies, including a systematic review, have shown that intramuscular prophylaxis is more effective than oral penicillin at reducing recurrent streptococcal pharyngitis, ARF and subsequent RHD.^{8 11–13} In New Zealand, where RF is endemic among indigenous populations, penicillin every four weeks has dropped the ARF recurrence rate to $0.6/100$ patient years.^{14 15} Compliance rates of $>90\%$ have been the norm. One study from Taiwan proposed that every 3 weeks is better than every 4 weeks for intramuscular (IM) penicillin;¹⁶ the evidence base for IM penicillin every 3 weeks rather than every four has been challenged in recent years. Only those with a definite recurrence on 4-weekly penicillin are recommended for a 3-weekly regimen.¹⁷

Our patient has taken oral penicillin two times per day for a total of 10 years. While compliance is difficult to assess objectively, our patient's team was satisfied at each cardiological review with the parent-reported and patient-reported compliance with her prescribed oral prophylactic regimen. At presentation, echocardiography showed only trivial valvular regurgitation with normal left ventricular function. Our patient was comprehensively reviewed throughout childhood and there was no documentation of any intercurrent GAS pharyngitic

episodes or any episodes suggestive of an ARF recurrence. In addition, the parents and the patient knew to seek medical attention if any symptoms of such episodes occurred. Therefore, while it remains an outside possibility that episodes of recurrent ARF/GAS pharyngitis went unreported, it is most likely that the progression of her mitral valve disease was mediated through subclinical episodes of reinfection with GAS. Secondary prophylaxis for this patient failed.

This case highlights some of the challenges for clinicians who deal with RF in areas where it is uncommon, such as the UK. Clinicians' experience with RF in these areas may be limited. Oral penicillin may be recommended as it seems kinder to the patient: it may be more difficult for the health professional to recommend painful injections, and more difficult for the family to accept the recommendation, if they are one of the few children in the region receiving such injections. Secondary prophylaxis is a simple concept, but delivery is often problematic.

In countries where RF is endemic, secondary prophylaxis is delivered as part of a formal community programme with a central register of patients and a dedicated coordinator. Funding for delivery of penicillin is well sanctioned. Within this environment, the evidence-based practice for intramuscular penicillin is accepted by the patient (usually a child) and their family and by involved health professionals. Penicillin is administered every 28 days by nurses who build up a rapport with the child with injections administered at school or in the community. Long-term compliance is reinforced at each follow-up. These programmes have been associated with reduced rates of ARF recurrences and high degrees of adherence to secondary prophylaxis regimens.^{14 15 17} These resources may not be available in countries with a low incidence of ARF.

There will be long-term repercussions for secondary prophylaxis failure in this patient. Pregnancy outcomes for warfarinised women with prosthetic valves are poor;¹⁸ although she does not require formal anticoagulation at this point, prosthetic valve implantation could still be required within her reproductive years.

This case also reminds us that those patients who are free from RHD or who have minimal evidence of carditis at first presentation still remain at a risk of ARF recurrence and subsequent cardiac damage. More than half of the patients who present with Sydenham's chorea with no initial evidence of carditis ultimately develop RHD.¹⁹ As demonstrated by our case, the recurrences that lead to RHD may be subclinical.^{5 20}

Learning points

- ▶ This case emphasises the current body of evidence that oral prophylaxis regimens are less effective than intramuscular penicillin regimens in preventing recurrences of acute rheumatic fever (ARF) and progression of rheumatic heart disease (RHD).
- ▶ Clinicians in low-incidence countries must follow best practice guidelines in the management of ARF/RHD and remain particularly cognisant of the superior efficacy of intramuscular penicillin, despite a relative paucity of local guidelines and health community supports to aid in its administration.
- ▶ Despite its rarity in these areas, the cardiac sequelae of ARF can be just as devastating and may be silent in the earlier stages.

- Regardless of ethnicity or endemicity, prescribing the most effective secondary prophylaxis regimen is essential.

Contributors All the authors made a substantial contribution to the writing of this case report and in the final approval of the case report. SMM-B and NJW performed the literature search. SMMG-B planned, drafted and revised the paper. HMP revised and critically appraised the draft paper at multiple stages. PFC and NJW were involved in the management of the case and patient in question. PFC and NJW are the guarantors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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