CASE REPORT

Atrioventricular block related to liposomal amphotericin B

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Accepted 13 May 2014

SUMMARY

Atrioventricular block can occur in normal children, young adults or athletes. It is also associated with underlying heart disease or occurs as a drug adverse effect. Amphotericin B is used in the treatment of invasive fungal infections. Cardiac toxicity is a rare adverse reaction. We report the case of a 9-month girl, admitted in the paediatric intensive care unit with cytomegalovirus pneumonitis. During hospitalisation the patient developed a systemic fungic infection and was medicated with liposomal amphotericin B. On the third day of treatment she began repeated episodes of bradycardia with spontaneous reversion. The investigation revealed a second-degree atrioventricular block. We excluded the misplacement of the central catheter, myocarditis or structural cardiomyopathy and suspended amphotericin. After 8 days, the bradycardia episodes ceased what was consistent with the drug's half-life. Amphotericin cardiotoxic mechanism is still unclear. It may be related with alteration of myocardial membrane depolarisation.

BACKGROUND

Bradycardia is defined as a heart rate below the lowest normal values set for age. Although less common in children than adults, it can occasionally cause significant morbidity and sudden cardiac death.[1] The risk of death in untreated children with complete block of the atrioventricular (AV) node is 5–8%.[2] It is therefore important to identify children at risk and who might benefit from therapeutic intervention. When an AV block is identified, it is relevant to categorise it according to the ECG findings. The conduction may be slowed without missed beats (first degree), intermittent with missed beats (second degree) or absent with complete dissociation of the atrial and ventricular activity (third degree). Wenckebach first described the AV block as a progressive delay between atrial and ventricular contraction with the eventual failure of an atrial beat to reach the ventricle.[3] Later, Mobitz divided the second-degree AV block in type I (progressive PR interval prolongation that precedes a non-conducted P wave) and type II (PR interval unchanged before a non-conducted P wave).[4] Second-degree AV block usually does not produce symptoms and can occur in normal children and young adults or athletes.[5 6] However, it is also associated with an underlying heart disease such as intrinsic AV nodal disease, structural cardiomyopathy, myocarditis, endocarditis, acute inferior myocardial infarction, after cardiac surgery, ablation or catheterisation procedures and secondary to hypothyroidism or hyperthyroidism.[7] Impaired AV conduction is also a recognised adverse reaction of digitalis, calcium channel blockers, amiodarone, adenosine and β-blockers.[7] A variety of other drugs can more rarely impair AV conduction.

Amphotericin B is a polyene antifungal agent used as 'gold standard' in the treatment of invasive fungal infections since the 1960s.[8] The major reasons for this lasting acceptance are its broad spectrum and the relatively few examples of mycological resistances to the drug.[9] The main adverse reactions associated with amphotericin are nephrotoxicity, electrolyte abnormalities (hypokalaemia, hypomagnesaemia and hyperchloremic acidosis), infusion-related reactions (fever, nausea, vomiting, chills, rigours) and normocytic, normochromic anaemia.[9 10] Lipid-based formulations of amphotericin have been introduced in an attempt to reduce the toxicities associated with amphotericin B deoxycholate. On the basis of animal models and clinical studies, these formulations reduce the risk of amphotericin B-related nephrotoxicity and infusion-related reactions.[11 12]

CASE PRESENTATION/INVESTIGATIONS/TREATMENT

We report the case of a 9-month old girl, ex-premature of 35 weeks, with a history of three previous hospitalisations caused by uncomplicated infections (fever without focus, acute bronchiolitis, gastroenteritis) and failure to thrive since 6 months of age. At the reported hospitalisation, she was admitted at the emergency department with an acute respiratory infection presented by malaise, refusal to eat, tachypnoea and hypoxaemia. In view of clinical deterioration with the developing of an acute respiratory distress syndrome, she was transferred to the paediatric intensive care unit and was mechanically ventilated. The investigation revealed a cytomegalovirus (CMV) pneumonitis (positive IgM serology plus bronchoalveolar lavage and urine isolation of the virus). The immunological investigation was negative. She was medicated with ganciclovir, human unspecific immune globulin and CMV-specific immunoglobulin. The patient began gradual clinical recovery and was extubated from mechanical ventilation. On the 14th day after admission she began to have fever with increase of the laboratory inflammatory parameters. The peripheric and central line haemocultures were positive, with isolation of *Candida parapsilosis*. The patient was medicated on the 16th day with liposomal amphotericin B (3 mg/kg/day). The femoral central line was removed and a right subclavian

To cite: Sanches BF, Nunes P, Almeida H, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-202688

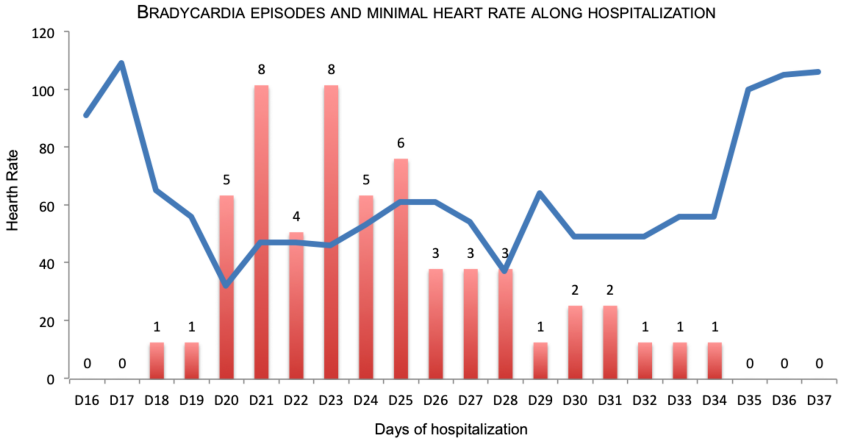

Figure 1 Graphic representation of the bradycardia episodes along hospitalisation. The blue line represents the evolution of minimal heart rate value and the red columns represent the number of bradycardia episodes per day since the 16th to the 37th days of hospitalisation (number of the episodes in the top of each column). Amphotericin therapy was started on the 16th day and was suspended on the 27th day of hospitalisation.

central line was placed. On the 18th day after admission she began short-term episodes of bradycardia, all asymptomatic, with spontaneous reversion to normal sinus rhythm (evolution of episodes during hospitalisation represented in figure 1). The remainder of the cardiovascular physical examination was normal. Creatine kinase, troponin, calcium, potassium and magnesium were between normal values. The ECG was normal and the echocardiography did not show any evidence of myocarditis, myocardial infarction or structural cardiomyopathy. This examination also revealed an intra-atrial position of the central catheter (figure 2), which was then repositioned to an extra-cardiac position (figure 3). A 24 h ECG monitoring (Holter examination) was performed and revealed a second degree atrioventricular block, Mobitz type 1 alternating with Mobitz type 2 (figure 4). At this time, the patient was only medicated with liposomal amphotericin B (third day of treatment) and with ganciclovir (15th day of treatment). Liposomal amphotericin B was suspended and the patient began fluconazole therapy. Along the following 7 days the number of bradycardia episodes per day diminished progressively (figure 1). Eight days after liposomal amphotericin B interruption the episodes ended. We repeated the 24 h ECG monitoring which was normal, without evidence of any rhythm block.

OUTCOME AND FOLLOW-UP

In the 6 months follow-up after this hospitalisation the patient did not repeat any episode of bradycardia or any cardiovascular event. However, she was readmitted with another respiratory infection. All immunological investigation till present date was inconclusive.

DISCUSSION

In this case we report the diagnosis of adverse reaction to liposomal amphotericin B, which was postulated after exclusion of the main possible causes of bradycardia, in particular of second-degree AV heart block. The major hypotheses considered in the differential diagnosis were: viral myocarditis, misplacement of the central venous catheter, structural cardiomyopathy, intrinsic AV nodal disease and adverse pharmacological reaction.

On the basis of the patient medical history of recurrent infections and the confirmed CMV pneumonitis, we suspected that our patient had a primary immunodeficiency. That led us to consider viral myocarditis as a possible bradycardia aetiology. The immunological investigation performed till the present date was inconclusive. Nevertheless, there are also reports of CMV myocarditis even in immunocompetent patients.[13 14] However, the combination of an asymptomatic patient with negative cardiac enzymes and no suggestive evidence of myocarditis in the ECG or the echocardiogram performed gave less consistency to this hypothesis.

The misplacement of the subclavian vein catheter was confirmed by the echocardiogram performed that showed an intra-atrial position of the central line. Cardiac dysrhythmias, most often premature atrial or ventricular contractions are the recognised complications during central venous access procedures.[15 16] These events are related with guidewire insertion (the Seldinger technique) or catheter migration with patient

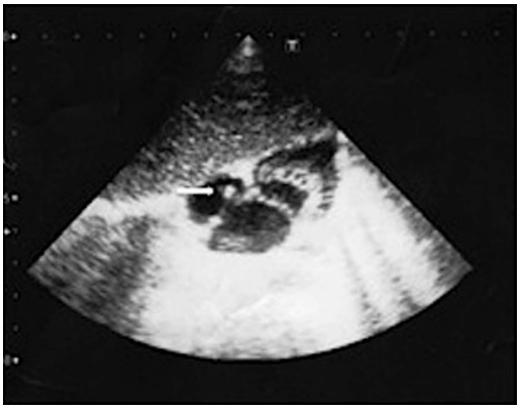

Figure 2 First echocardiography. The white arrow points to the central venous catheter tip located inside the right atrium.

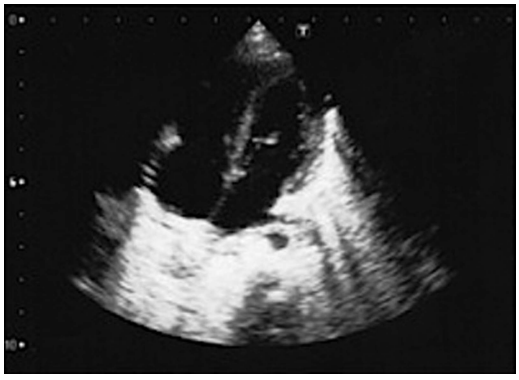

Figure 3 Second echocardiography. No evidence of misplacement of the central venous catheter after repositioning.

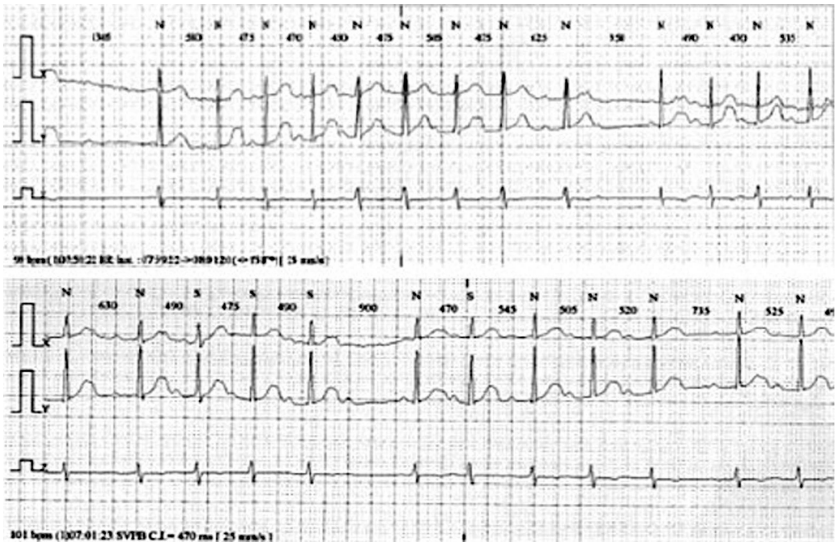

Figure 4 Holter examination. The second-degree heart block Mobitz type 1 is noted in the upper image and the Mobitz type 2 is noted in the lower image. Along the 24 h was recorded a sinus rhythm (maximal heart rate: 145; medium heart rate: 82; minimal heart rate: 54).

movement with subsequent contact with the endocardium. Although less frequently,[16] right bundle branch blocks can also occur, probably related to the bundle branch's superficial position in the right ventricular endocardium.[8] This arrhythmias and conduction abnormalities should resolve when the tip of the catheter is pulled back a few centimetres.[16 17] We repositioned our patient's catheter and confirmed its extracardiac position with echocardiography. Despite that, the patient continued the bradycardia episodes.

There was also no evidence of a structural cardiomyopathy noted in the echocardiograms performed. Since these bradycardia episodes were stable (without signs of haemodynamic compromise) we did not perform an electrophysiological study to exclude an intrinsic AV nodal disease before excluding a possible pharmacological adverse reaction.

Cardiac toxicity is a rare adverse reaction associated with amphotericin B.[18–20] Ventricular arrhythmias and bradycardia have been reported in acute overdoses but also with conventional dosages and infusion rates.[21 22] Electrolyte abnormalities such as hypokalaemia and hypomagnesaemia related to amphotericin B may play a role. However, case reports of arrhythmias in patients with normal concentration of potassium and magnesium medicated with amphotericin suggest that it may be directly cardiotoxic.[9 23] Animal experiments have shown that amphotericin B can result in prolongation of the PR interval, prolongation of the action potential with decrease in its amplitude.[24–26] The drug mechanism of action is based on the binding of the hydrophobic moiety of the amphotericin B molecule to the ergosterol present in fungal cell membrane, producing an aggregate that forms transmembrane channels. These defects cause an increase in permeability to protons and monovalent cations with subsequent cytoplasmic leakage (mainly potassium) that leads to fungal cell death.[27] Despite the more avid binding to ergosterol, amphotericin B also has the capacity of binding to the cholesterol of mammalian cell membranes, which is responsible for a major fraction of its toxic potential.[28] Cardiac toxicity may be caused by the abolition of the slow inward calcium channel current and alteration of membrane depolarisation by the referred pores in the myocardial membrane.[20 26]

In our patient, after the interruption of the liposomal amphotericin B, the number of bradycardia episodes progressively diminished along the following 7 days and stopped after 8 days. The AV blockage resolution was confirmed with the 24 h ECG monitoring performed 9 days after the drug suspension. This evolution is consistent with the long terminal half-life of the drug (152 h±116 h).[29]

There is no specific treatment for amphotericin B toxicity. The drug is not removed by haemodialysis with conventional or high-flux dialysis membranes.[30] As the cardiac toxicity signs become evident, after the suspension of amphotericin administration the approach consists of supportive therapy directed at correcting electrolyte abnormalities, anaemia and dialytic support for renal failure. It is also important to exclude all reversible causes of AV block and remove them. Transient pacemaker placement is reserved to symptomatic or haemodynamically unstable patients.

Learning points

- Second-degree atrioventricular (AV) block may occur in normal children, but it can be secondary to intrinsic cardiac disease or be related with an adverse drug reaction. All reversible causes should be excluded.
- Cardiac toxicity is a rare adverse reaction related to liposomal amphotericin B. However, it should be considered in a patient with recent bradycardia, AV block or ventricular arrhythmias.
- There is no specific treatment for amphotericin B toxicity. After the drug suspension, it is relevant to remember that cardiac toxicity signs can persist for several days, consistent with the long terminal half-life of the drug (152 h±116 h).

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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