ORIGINAL ARTICLE

Spectrum of Infections in Splenectomised Thalassaemia Patients

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SUMMARY

Splenectomised thalassaemia patients are at risk of developing sepsis. As the infection may be life-threatening, treatment should be sought and given promptly. A retrospective study was performed amongst our thalassaemia major patients who were splenectomised. The vaccination status of each patient and the types of infections seen were reviewed to obtain a local perspective. In our cohort of 49 splenectomised patients, 25 patients required hospitalization for the treatment of infection. There were a total of 40 febrile episodes within this hospitalised group of which 27.5% were microbiologically documented infection with bacteraemia. The predominant causative organisms were gram negative rods and three patients succumbed to overwhelming septicaemic shock as a result of delayed presentation. Sixty percent of the febrile episodes were clinically documented infection and comprised mainly upper respiratory tract infections. Based on the spectrum of infections seen, there is a need to improve the patients' awareness level so that early treatment is sought. There is also a need to re-address the approach towards vaccination in this immunocompromised group of patients by administering a booster pneumococcal and influenza vaccination in an attempt to reduce morbidity.

KEY WORDS:
post-splenectomy sepsis, thalassaemia, gram negative infections

INTRODUCTION

Thalassaemia is the commonest single gene disorder in Malaysia; the carrier rate is estimated to be between 3 to 5% with an annual incidence of 120 to 350 new cases of thalassaemia major.[1] As a proportion of these patients may require splenectomy at some point in time, it is important that clinicians are aware of its complications so that treatment can be instituted promptly. Although infection is reportedly highest within the first two years following splenectomy in these individuals, the risk is actually life – long. This article is a review of the pattern of infections seen in all of our thalassaemia patients who had undergone splenectomy.

MATERIALS AND METHODS

This retrospective review was conducted over a period of 6 months, from September 2006 till February 2007. Based on the Thalassaemia Registry, the total number of thalassaemia patients on follow-up at our Paediatric Haematology and Oncology Unit is 156 patients. From this group, 18 are alpha-thalassaemia (predominantly HbH disease) and the remaining 138, beta-thalassaemia, of which 82 are HbE-beta thalassaemia. From this pool of 138 beta-thalassaemia patients, a total of 51 patients were identified to have had a splenectomy performed. These patients' hospital records were subsequently examined and reviewed to determine their demographic data, date of splenectomy, history of infections, existing co–morbidities and whether pre–splenectomy vaccinations and prophylactic antibiotics were given.

RESULTS

From the total of 51 thalassaemia patients who underwent splenectomy, two had to be excluded as the relevant portion of hospital records were missing. Of the remaining 49 patients, 24 were homozygous beta thalassaemia and the remaining 25 were HbE – beta thalassaemia. The majority (61.2%) of these patients underwent splenectomy within 10 years of diagnosis. The mean age at which splenectomy was performed was 8 years with a range of 4 to 22 years; one patient was below the age of 5 years. The indication for splenectomy in all these patients was increasing spleen size with features of hypersplenism in association with increased transfusion requirements.

Following splenectomy, all 49 patients were given prophylactic oral penicillin. The majority of these patients, i.e. 40 patients (81.6%) were vaccinated 4 to 6 weeks before splenectomy; 26 (65%) were vaccinated with both pneumococcal and *Haemophilus influenzae type b* (Hib), and 14 (35%) received only the pneumococcal vaccine. The vaccination status of the remaining 12 patients was not documented.

A total of 25 (51%) patients required hospitalization for treatment of infection. From this group of 25 patients, 11 patients (44%) had received both vaccinations, whereas the remaining 14 patients (56%) received only the pneumococcal vaccine. Five (20%) were splenectomised within the past one year. Based on data collected for the hospitalized group, the total number of documented febrile episodes was more than the number of patients, i.e. 40 febrile episodes amongst a total of 25 hospitalised patients. This was because there were eight patients who had recurrent febrile episodes of whom three had co-morbidities of diabetes mellitus and cardiomyopathy secondary to iron overload. However, only two of the eight patients were below 12 years of age.

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Of the 40 febrile episodes, 15 were microbiologically documented infection (MDI), 24 were clinically documented infections (CDI) and only one was fever of unknown origin. From the group of MDI without bacteraemia, the causative organism was isolated from incision and drainage of abscesses: only one was a gram positive organism (*Staphylococcus aureus*) which was isolated from an intramuscular abscess. The remaining three were gram negative organisms isolated from the parapharynx, liver and central venous catheter (two were Klebsiella species and one Pseudomonas species). Whereas for the group of MDI with bacteraemia, there were more gram negative isolates compared to gram positive, i.e. seven compared to four respectively. Combining both groups of MDI (with and without bacteraemia), the predominant pattern of causative organism within this group of hospitalized patients was gram negative, i.e. 10 of 15 episodes.

For the CDI group (Table I), this mainly comprised infections involving the upper (e.g. exudative tonsillitis) and lower respiratory tract (bronchopneumonia and empyema). This group of hospitalized patients had either already increased the dose of penicillin from prophylactic to treatment dose themselves, or had been given a course of antibiotics by general practitioners prior to the admission. The majority of the respiratory tract infections were empirically treated with intravenous crystalline penicillin. Although throat swabs for detection of respiratory viruses and bacteria were not done routinely for those admitted with symptoms of respiratory tract infection, a significant proportion of upper respiratory tract infections are usually viral in origin.

From the group of 25 hospitalised patients, three died as a result of overwhelming septicaemia: 2 from *E. coli* septicaemia and the other from cholera. All three were admitted in a state of hypovolaemic shock requiring admission to the intensive care unit. All were adult patients who had undergone splenectomy more than 5 years prior to the fatal episode.

DISCUSSION

Patients who are splenectomised are often referred to as being immunocompromised. This is because splenic macrophages are responsible for the filter and phagocytosis of bacterial and blood borne pathogens. Regular blood transfusion also results in immunomodulation. Furthermore, the use of iron chelation therapy and infection by organisms (*e.g. Yersinia enterocolitica*) which thrive in high iron condition are additional risk factors. Hypersplenism is an absolute indication for splenectomy in thalassaemia major patients. In a review by Bisharat et al comprising 78 published articles on a total of 19680 splenectomised patients, the incidence of infection was highest amongst patients with thalassaemia major, i.e. 8.2%. [2] As the mortality rate for overwhelming post–splenectomy sepsis (OPSI) is high, i.e. up to 50%, early recognition and prompt intervention is indicated. [3]

In our cohort of patients, the number of homozygous beta – thalassaemia and HbE beta – thalassaemia patients is comparable, with the majority of the latter group being thalassaemia major phenotypically. All of these patients had splenectomy after the age of 5 years (except for one), which is in line with our local policy, as those below this age are more prone to invasive infections by encapsulated organisms. It is also not surprising that all of the patients received penicillin, as the policy within our unit is life-long penicillin prophylaxis following splenectomy, in keeping with the revised guidelines prepared by the British Committee for Standards in Haematology (BCSH).[4] The issue of compliance was not addressed in this review as it is not only in retrospect but also subjective. A compliance study by Keenan et al reported that only 42% of 58 adult patients, who were splenectomised for various indications, were compliant based on a biological urine assay for penicillin.[5] Poor compliance was similarly reported amongst paediatric patients with sickle cell disease requiring penicillin prophylaxis. [5,6] Thus it is likely that many of our patients may have been non-compliant.

A significant proportion (81.6%) of our splenectomised patients was vaccinated. However, not all received *Haemophilus influenzae type b* vaccination because the vaccine was not readily available within the hospital until after February 1998 and none received the meningococcal vaccine as it is only recently available. *Haemophilus influenzae type b* was not isolated amongst our bacteraemic patients; this organism causes invasive acute respiratory diseases (e.g. bronchopneumonia, epiglottitis) with significant morbidity that is more prevalent within the first five years of life. As our cohort of patients were predominantly beyond 12 years of age, it is not surprising that *Haemophilus influenzae type b* was not isolated. Based on the revised BCSH guidelines, all splenectomised patients should ideally receive the pneumococcal, *Haemophilus influenzae type b* and meningococcal (group c) conjugate vaccines. In addition to this, influenza immunization should be given and re-immunisation with pneumococcal vaccine is recommended every five to ten years as dictated by the levels of antibody titres.4 In a Danish population-based study of 538 splenectomised patients, only 60% had been given the pneumococcal vaccine pre-operatively; whereas in a more recent audit amongst patients undergoing elective splenectomy in Scotland, only 13% of patients received all three vaccines prior to surgery. [3,7] As vaccination has been shown to reduce the risk of bacteraemia from any cause beyond the postoperative period, it is indeed imperative that the recommended vaccination policy is adhered to. Our local (Malaysian Society of Paediatric Haematology and Oncology) guidelines recommend that vaccination against pneumococcal, *Haemophilus influenza type B* (Hib) and *Neisseria meningitidis* (if available) be given at least 4 to 6 weeks prior to surgery; recommendation for a booster dose of pneumococcal vaccine is however not included. [8] The recently available seven-valent conjugate pneumococcal vaccine has been shown to be more immunogenic. However, based on the BCSH guidelines, its role needs to be defined further.

From our review, although there is a lack of laboratory confirmation of viral aetiology, the fact that 58.3% of CDI were upper respiratory tract infections should not be dismissed too readily; hence administration of influenza vaccine should be considered. This is again in keeping with the recommendation made by the BCSH. It is interesting to note that our patient with streptococcus septicaemia did receive the pneumococcal vaccine prior to splenectomy but as she did not receive any booster vaccination, her antibody titre level presumably declined over the years making her susceptible to infection.

In our cohort of patients, there was a predominance of gram negative organisms amongst those with a severe infection. Recently published studies also show a similar trend of overwhelming sepsis due to gram negative bacilli, which is presumably related to the current recommended

vaccination guidelines and use of penicillin prophylaxis. In a review by Ghosh et al of 46 thalassaemia patients who were splenectomised, all documented overwhelming infections were caused by gram negative organisms such as Klebsiella, Pseudomonas, Aeromonas and Campylobacter.[9] Similarly, in a review by Ejstrud et al, Enterobacteria was the predominant (45%) causative organism amongst a cohort of 561 patients who were splenectomised for various indications.[7]

OPSI is reportedly most common within the first 2 years following splenectomy; however, it is still reported decades later.[10] All the three patients who died were adults who had undergone splenectomy more than 5 years prior to the fatal episode. Only one had a co-morbidity of cardiomyopathy secondary to chronic iron overload, the remaining two patients did not have any co-morbidity such as diabetes mellitus. Based on this, one should not be complacent when treating a splenectomised patient who presents with a febrile episode, regardless of the time interval from splenectomy as the life time risk of 5% is still clinically significant.[11] Although not all of the febrile episodes were clinically severe, there may also be considerable impact from the psychosocial aspects such as schooling and employment, as hospitalization was deemed necessary in 51% of our patients. As it is evident that splenectomy may cause mortality, optimizing the transfusion regime will help obviate the need for splenectomy in future.

Another important point to note is the late presentation of the three patients who succumbed. These patients had been unwell more than 24 hours prior to admission and were in a clinical state of hypovolaemia. There is a need to reinforce patient education and level of awareness so that treatment is promptly sought upon occurrence of a febrile episode. Although our policy is to increase the dose of prophylactic penicillin to therapeutic doses should the patient develop fever with URTI symptoms, the patients are still advised to seek early treatment should there be no clinical improvement. Some authors have also recommended that patients be given self-prescribed or stand-by antibiotics, but this should only be considered in selected cases where there is already a satisfactory level of patient comprehension. [11]

CONCLUSION

Overwhelming sepsis, particularly gram negative infection, is a recognized complication in splenectomised thalassaemia patients. Comprehensive patient counselling in addition to prompt initiation of treatment is therefore warranted in order to prevent this potentially fatal complication.

Table I:
Spectrum of organisms isolated in bacteraemic patients

Organism	Number of episodes
Gram positive	
Staphylococcus aureus	2
Enterobacteriaciae	1
Streptococcus pneumoniae	1
Gram negative	
Klebsiella spp	1
Klebsiella pneumoniae	1
Pseudomonas spp	1
Escherichia coli	2
Vibrio cholerae	1
Gram negative rod (not identified)	1
Total	11

Table II:
Spectrum of clinically documented infections

Type of infection	Total number of episodes (%)
Upper respiratory tract infection	14 (58.3)
Lower respiratory tract infection	2 (8.3)
Gastroenteritis	1 (4.2)
Urinary tract infection	3 (12.6)
Meningitis	2 (8.3)
Others (ruptured appendicitis with peritonitis; left mastoid abscess)	2 (8.3)
Total	24

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REFERENCES

1. Training Module for Thalassaemia Counsellors, July 2009. Division of Family Health Development, Ministry of Health Malaysia.
2. Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. J of Infection 2001; 43: 182-6.
3. Newland A, Provan D, Myint S. Preventing severe infection after splenectomy. Br Med J 2005; 331: 417-8.
4. Davies JM, Barnes R, Milligan D. Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. Clinical Medicine 2002; 2: 440-3.
5. Keenan RD, Boswell T, Milligan DW. Do post-splenectomy patients take prophylactic penicillin? Br J Haematology 1999; 105: 509-10.
6. Cummins D, Heuschkel R, Davies SC. Penicillin prophylaxis in children with sickle cell disease in Brent. Br Med J 1991; 302: 989-90.
7. Ejstrud P, Kristensen B, Hansen JB, et al. Risk and patterns of bacteraemia after splenectomy: A population based study. Scand J Infect Diseases 2000; 32: 521-5.
8. R Jamal (ed). Guidelines for the management of thalassaemia. (1st ed). Universiti Kebangsaan Malaysia, 2008.
9. Ghosh K, Daar S, Hiwase D, Nursat N. Primary pseudomonas meningitis in an adult, splenectomised, multitransfused thalassaemia major patient. Haematologia 2000; 30: 69-72.
10. Waghorn DJ, Mayon-White RT. A study of 42 episodes of overwhelming post-splenectomy infection: Is current guidance for asplenic individuals being followed? J of Infection 1997; 35: 289-94.
11. Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. Clin Microbiology & Infection 2001; 7: 657-60.