Ann Hematol (1999) 78:524–528

CASE REPORT

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Frequency of very late fatal sepsis after splenectomy for hereditary spherocytosis: impact of insufficient antibody response to pneumococcal infection

Received: January 4, 1999 / Accepted: May 10, 1999

Abstract Very late sepsis in splenectomized patients with hereditary spherocytosis has been seen rarely up to now; the frequency and the immunodeficiency causing it are largely unknown. Within the past 7 years we have learned of four cases of sepsis or meningitis (three fatal) in adult patients with hereditary spherocytosis who had been splenectomized years earlier. The estimated frequency of very late postsplenectomy infections is 0.69 cases of sepsis or meningitis in 1000 patient-years (0.46 deaths in 1000 patient-years). Pneumococci were proven in two patients. The surviving patient showed low antibody titers against pneumococcal serotypes even after pneumococcal meningitis and subsequent vaccination. There have been several reports of an insufficient response to pneumococcal vaccination in patients with severe infections. We recommend determination of pneumococcal antibody titers after immunization in every splenectomized patient: Nonresponders to vaccination may be at high risk for overwhelming postsplenectomy infection. Our data demonstrate that there is a lifelong risk for severe postsplenectomy infections and therefore the lasting need for immediate antibiotic therapy in any case with sudden onset of high fever.

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Key words Hereditary spherocytosis · Postsplenectomy · Sepsis · Overwhelming postsplenectomy infections · Pneumococci

Introduction

Splenectomy during childhood and adolescence is necessary in many cases of moderate to severe hereditary spherocytosis [1]. Following splenectomy the risk of overwhelming infections is increased [2–6]; 93% of infections occur during the first 3 years after splenectomy [2] and continuous oral penicillin prophylaxis is recommended for this period. However, even years after splenectomy sepsis can occur [7]. Postsplenectomy-sepsis starts with sudden onset of high fever, occasionally preceded by a short period of flu-like symptoms (headache and vomiting). The course is fulminant: 40–50% of the patients die [8]. *Streptococcus pneumoniae* is by far the most frequent organism, followed by *H. influenzae*, staphylococci, meningococci and others. Children under the age of 5 years at the time of splenectomy have a particularly high risk of sepsis [9]. The high risk of infections with encapsulated bacteria in splenectomized patients is most likely caused by an impaired immune defense; the exact nature of this defective immune response is unknown.

Within 10 years we have learned of four adult patients with spherocytosis who developed fatal/severe sepsis and/or meningitis 16–28 years after being splenectomized. The tragic events were reported to us while we were treating their children with spherocytosis. Pneumococci were detected in two of them. Only one patient had been vaccinated against pneumococci.

Methods

Total IgG antibodies against pneumococcal serotypes 3, 4, 9V, and all 23 serotypes which are combined in the vaccine (Pneu-

Table 1 Sepsis and meningitis after splenectomy in patients with spherocytosis

Patient	Age (years) at infection/death[a]	Years after splenectomy	Late post-splenectomy infection (course)	Blood and CSF culture	First antibiotics (h after onset of fever)	Pneumococcal immunization
S.I.	29 (1995)	28	Sepsis (lethal)	Negative (under penicillin)	Penicillin V (3)	No
S.N.	46 (1990)	24	Sepsis and meningitis (lethal)	Pneumococci	Tetracycline p.o. (8)	No
I.N.	24 (1985)	16	Sepsis (lethal)	Not done	None	Yes
V.J-M.	30 (1990)	22	Meningitis (full recovery)	Pneumococci	Penicillin V (48)	No

[a] Actual year is indicated in parenthesis

movax) were determined by ELISA, as described by Siber et al. [10] and modified by Sanders et al. [11].

From 1989 to 1995, data from 330 children with hereditary spherocytosis were prospectively collected. In addition, we asked whether splenectomy had been performed in close relatives and if complications and side effects after surgery had occurred. We received information about 169 splenectomized relatives, among them the three patients with severe infections presented here in detail (Table 1).

Case reports

Case 1

A 29-year-old patient, S.I., was admitted to an outer hospital 1995 with septic shock (high fever, tachycardia, cyanosis, and cardiovascular centralization). The patient had been splenectomized at the age of 1 year because of hereditary spherocytosis. Neither had she received pneumococcal immunization, nor was she under prophylaxis with antibiotics when she developed high fever the night before admission to hospital. She had felt sick the day before. At 4 a.m. her temperature was around 40 °C. She consulted a physician, who put her on penicillin V (phenoxymethyl penicillin). During the following 9 h she started vomiting. When she was admitted to the intensive care unit, 12 h after the onset of fever, she was still conscious. Initially she received penicillin G (10 million I.U. benzyl penicillin), later on gentamicin (240 mg/day) and ceftriaxone (2 g/day). Shortly after admission she required intubation and mechanical ventilation. High doses of catecholamines did not prevent cardiovascular collapse and she developed severe disseminate intravascular coagulation. Despite the intensive medical care and early antibiotic treatment, the patient died 30 h after the onset of fever. Autopsy was denied.

Case 2

A 46-year-old patient, S.N., who had been splenectomized 24 years earlier because of hereditary spherocytosis at the age of 22 years, was admitted to an outer hospital. She was not immunized against pneumococci. She reported having had severe headache in the morning of the same day and she had a temperature of 39.6 °C and chills. Eight hours after the fever had started she received tetracycline p.o. and metamizole from the physician on call. Six hours later she became somnolent. On admission to the hospital she was stuporous and required mechanical ventilation for respiratory insufficiency. She showed signs of meningism and muscular hypotonia. Cranial computed tomography revealed a cerebral edema without signs of subarachnoid hemorrhage or tumor. Cerebrospinal fluid was purulent. She was treated with cefotaxim and gentamicin. Despite intensive care she died the next morning, about 24 h after the first signs of disease had appeared. The autopsy showed a bacterial meningitis and a cerebral edema. Cultures of cerebrospinal fluid as well as blood were positive for pneumococci. No infections were found in her ears, lungs, or sinuses.

Case 3

A 24-year-old woman, I.N., had been splenectomized for hereditary spherocytosis at the age of 8 years. While her first affected child was under regular follow-up, the mother was vaccinated against pneumococci and advised to take oral penicillin daily in case of febrile illness. Three years later, 9 weeks after having delivered a second child, she had a mild flu but considered oral penicillin inappropriate while breast-feeding; a few days later she complained about having headaches and chills and was prescribed aspirin by a physician. A few hours later she became unconscious and died the same day, 16 years after her splenectomy, in spite of resuscitation maneuvers.

Case 4

The 30-year-old patient V.J-M., who had been splenectomized at the age of 9 years because of hereditary spherocytosis, developed a high fever of about 41 °C and severe headache. He had never received penicillin prophylaxis, nor was he vaccinated against pneumococci. At 3 p.m., 2 days after the onset of fever, the patient was found at home by his wife, disoriented and unable to walk without help. On admission to the hospital he was stuporous and had a distinct meningism, slightly dilated pupils, and slow pupillary reflexes. Cerebrospinal fluid was purulent with the growth of pneumococci. Penicillin G (10 million I.U. three times per day i.v.) was started and the patient recovered without any cerebral damage. The total antipneumococcal titer determined 3 years after the meningitis was low (757 arbitrary units (U)/ml; protective limit: >1000 U/ml). In addition, only a slight increase to 855 U/ml was detected after vaccination. IgG-subclass determination showed normal results.

Serotype specification showed insufficient titers below 20 U/ml for nine of 23 pneumococcal antigens (Fig. 1) [11]. This is especially remarkable for serotype 3, which is known to be highly immunogenic [2]. By far the highest value was determined for serotype 6B (682 U/ml), making this rare serotype the candidate for the cause of the preceding meningitis. Nevertheless, this titer is rather low, in view of the severe infection.

In addition, subsequent vaccination with a 23-valent vaccine (Pneumovax) years after infection yielded a relevant increase of pneumococcal antibody titers in only nine of 23 serotypes (Fig. 1). In particular, the response to serotypes 3, 4, and 9 failed; thus the patient fulfilled the criteria of nonresponse to pneumococcal vaccination [11, 12].

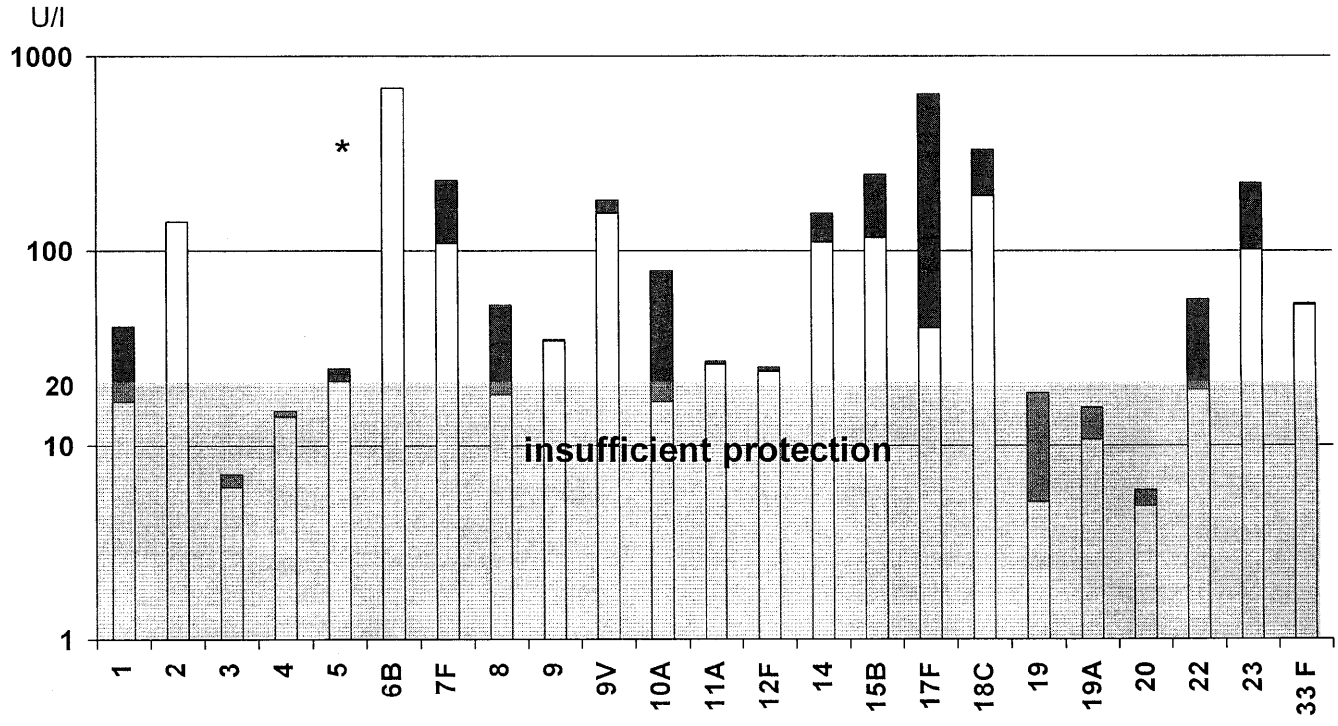

Fig. 1 Pneumococcal IgG antibodies after infection (*blank bars*) and vaccination (*gray bars*) in case 4. Serotype-specific antibody titers below 20 arbitary units, threshold for sufficient protection, were determined in nine of 23 pneumococcal antigens. The high value of antibodies against serotype 6B (*asterisk*) indicated that serotype 6B was the cause of the preceding meningitis. Sufficient response to vaccination, defined as at least doubling of the titer, failed in most serotypes

Discussion

We observed three cases of fatal sepsis/meningitis and one of severe meningitis in four parents with spherocytosis while we were treating their children. They had been splenectomized in childhood or adolescence, decades before the severe infection occurred. Pneumococci were proven in two cases and might also have been causative in the other two patients. Three of the patients (cases 1, 2, and 4) belonged to a group of 169 splenectomized relatives (average age 35 years) of children with spherocytosis who were treated in Göttingen. With a mean age of 9.4 years at the time of splenectomy, the average observation period was 25.6 years per patient. Thus the estimated frequency of postsplenectomy infection is 0.69 in 1000 patient-years (0.46 deaths in 1000 patient-years). The death risk for pneumococcal sepsis is increased several hundred-fold (the death rate from pneumococcal sepsis in Germany is 0.04‰; 37 of 880,000 deaths in 1996 [13]. The fraction of patients with severe infection in our observation (1.8%) is in fair agreement with reported data (2.4–3.5% infections in spherocytosis patients) [2].

In 1991 Konradsen and Henrichsen [14] reported that "pneumococcal infections in splenectomized children are preventable." This highly efficacious prevention was achieved by pneumococcal vaccination and antibiotic prophylaxis during feverish episodes. However, we come to a less confident conclusion with regard to adult patients than Konradsen and Henrichsen [14], considering the fulminant course in one of our patients who received penicillin treatment less than 3 h after the onset of fever. It seems that fatal sepsis might be virtually unpredictable, and thus antibiotic prophylaxis during feverish episodes may be too late. Moreover, compliance with the antibiotic prophylaxis becomes less as the time elapsed after splenectomy increases, and also many adults who were splenectomized before 1979 never received any pneumococcal vaccination. Furthermore, about 20–40% of the septicemias are caused by bacteria other than pneumococci (e.g., hemophilus, meningococci, staphylococci, and others) [2].

Pneumococcal vaccination without antibiotic prophylaxis does not provide full protection against late sepsis [15]. One of our patients died of sepsis despite previous vaccination that was performed after splenectomy. Although nowadays preoperative vaccination is routinely recommended, the antibody response to the immunization should not differ greatly between patients vaccinated prior to or after splenectomy [16]. In addition, we recently saw a couple who had lost their son to pneumococcal meningitis at the age of 6 years, 2.5 years after splenectomy. This patient had been vaccinated against pneumococci prior to splenectomy, was revaccinated 2 years later, and had received penicillin for 2 years after splenectomy. At least 19 severe postsplenectomy infections (six fatal, including our two cases) in vaccinated patients have been reported [17–22]. The major problem in the production of an effi-

cient vaccine is the existence of about 90 serotypes of pneumococci with different capsular antigens. Pneumococcal serotypes show a different geographic and age distribution [23]. This should be considered in studies on risk factors for pneumococcal infections as well as in studies on prevention of these diseases with pneumococcal vaccine [24]. Vaccination of children under the age of 2 years with the licensed unconjugated vaccine is not recommended.

There are two other major reasons for the increased risk of postsplenectomy infections.

Increasing penicillin resistance

There is growing resistance of pneumococci to penicillin [25]. There are several highly resistant pneumococci that may not respond to conventional doses, although in the majority of resistant strains the minimal inhibitory concentration is still well below the concentration achievable with standard penicillin dosages. The effects of penicillin resistance are most dramatic in patients with pneumococcal meningitis, because of the poor penetration of penicillin into the cerebrospinal fluid, which makes it difficult to achieve the effective drug concentration needed for highly resistant strains [25]. This might contribute to the reported failures of penicillin in meningitis [26]. High dosages of penicillin (up to 500,000 IU/kg body wt.) are recommended nowadays for treatment of bacterial meningitis in order to overcome intermediary resistant pneumococcal strains [27]. In fact, the survivor in our study was treated with high doses of penicillin (3×10 million I.U. i.v. daily.)

Polysaccharide-specific immune deficiency

One adult patient presented with low antibody response despite severe pneumococcal meningitis, probably due to serotype 6B. Later on, this patient was identified as a nonresponder to vaccination against pneumococci. In addition, we have previously published two cases of splenectomized patients with an insufficient response to pneumococcal vaccination who experienced severe pneumococcal infections [28]. An insufficient response to pneumococcal infection or vaccination is a characteristic of a recently described polysaccharide-specific immune deficiency [11, 29]; this selective immune deficiency predisposes the patients to pneumococcal infections [11]. It is frequently (but not in all cases) associated with an IgG-subclass 2 deficiency [30]. A reduced capacity of pneumococcal antibody production is observed temporarily within the first years of life and is responsible for the inefficiency of the unconjugated vaccine in infants and children under the age of 2 years. Some recent observations indicate that polysaccharide-specific antibody deficiency may also be more common in later childhood [11, 12]. In the meantime, a new conjugated pneumococcal vaccine has been developed to improve the response in children under the age of 2 years and also in older patients with polysaccharide-specific immune deficiency [31]. Unfortunately, this vaccine has so far not been available for patients prior to or after splenectomy.

Obviously, the best way to avoid severe infections is to restrict splenectomy to patients with moderate to severe spherocytosis. Therefore, we stratified spherocytosis into three classes of severity (mild, moderate, and severe forms of disease) according to the different hemoglobin and bilirubin concentration as well as the reticulocyte count. Patients with the mild form should not be splenectomized during childhood and adolescence [32].

Our data underline the need for careful lifelong "on demand" prophylaxis after splenectomy with a broad spectrum of antibiotics starting at the very beginning of high fever as well as pneumococcal vaccination. In addition, all patients should be checked for hemophilus antibodies, and vaccination should be given in case of insufficient titers. Most of the splenectomized parents of our patients are not aware of their increased risk of infection and have not received pneumococcal vaccination. Pediatricians caring for children with dominant hemolytic anemias have an increasing responsibility to ask about the vaccination state of parents who might have been splenectomized years before. Uninformed parents should in all cases be strongly advised to receive pneumococcal vaccination or revaccination. Determination of pneumococcal antibody titers split up into different serotypes [11] should be performed, and patients with insufficient immune response should receive continuous lifelong penicillin prophylaxis. Considering the increasing occurrence of penicillin resistance, partial splenectomy might be an appropriate alternative in spherocytosis [33–35].

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