

Does Vaccination of Splenectomized Patients against Pneumococci Induce Dextran-Reactive Antibodies?

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Abstract. Polyvalent pneumococcal vaccine containing polysaccharides from serotypes known to be cross-reactive with dextran was used for vaccination of 72 patients either shortly before or on the average 6.25 years after splenectomy. The titer of dextran-reactive antibodies was determined by passive hemagglutination before as well as 6 weeks and 6 months after vaccination. Already prior to vaccination the patients had moderately elevated titers of these antibodies and the titer was somewhat reduced during the study period. Small inter-group differences were observed but the titers of patients who had received cytostatic and/or radiation therapy did not appear to react differently to vaccination. It is concluded that this type of vaccine does not induce dextran-reactive antibodies when given to asplenic individuals.

Introduction

During studies on human antibodies to the polysaccharide capsule of some strains of pneumococci Neill et al. [1] found that the antibodies cross-reacted with their reagent sucrose. This was shown to be caused by a contaminant, later identified as dextran, a polysaccharide produced by *Leuconostoc mesenteroides* from sucrose. Dextran preparations are today widely used for a variety of purposes: substitution of blood or plasma loss, thromboprophylaxis, blood flow improvement etc. On rare occasions dextran infusions cause severe anaphylactic reactions, triggered by immune complex formation between dextran-reactive antibodies (DRA) and dextran [2, 3]. The origin of DRA still remains obscure, but immunization with dextran-resembling bacterial capsular polysaccharides (present in the pneumococcal vaccine) has been suggested as a cause as has the ingestion of commercial sucrose containing native dextran as a regular contaminant.

Overwhelming septicemia is a feared complication after splenectomy. Since pneumococci are the most frequent causative organisms vaccination has been suggested to reduce the risk, which seems to be increased permanently [4]. The aim of this study was to investigate if vaccination with polyvalent pneumo-

coccal vaccine of asplenic individuals and patients undergoing splenectomy turned them into potential dextran-reactors by inducing the formation of antibodies cross-reactive to dextran.

Patients and Methods

A search for splenectomies performed at the hospitals of Stockholm county (population 1.6 million) was made in the county's records for the years 1969-1983. Survivors still living in the region were offered free vaccination against pneumococci. The same offer was also given to all patients undergoing planned or emergency splenectomy at our department from 1983 onwards. Diagnosis, age at operation, and interval between operation and vaccination were registered for the patients accepting vaccination and presented in this study.

Vaccination against Pneumococci. This was performed consecutively as the patients were enrolled in the program from 1983 to 1985. Each patient received a single subcutaneous injection of a polyvalent pneumococcal vaccine, Pneumovax®, MSD; from August 1984 changed to Pneumovax® 23, MSD. The patients were vaccinated with 50 or 25 µg of capsular polysaccharide from each of 14 or 23 different pneumococcal capsular types, respectively. The vaccines contained polysaccharides from types known to be cross-reactive with dextran: 2 and 20 [5].

Determination of DRA. Serum samples were obtained before as well as 6 weeks and 6 months after vaccination. Serum samples were frozen at -70°C and analyzed in batches twice a year. The titer of DRA was determined by passive hemagglutination of stearyl-

Table 1. Changes in DRA titers of various subgroups

Subgroup	Before vaccination		At 6 weeks		At 6 months	
	n	$^{-2}\log$	n	Δ	n	Δ
Men	37	8.59	30	-0.67	27	-0.48
Women	35	7.97	28	-0.32	27	-1.15*
Trauma	18	8.44	14	-0.93	13	-1.15*
Iatrogenic	13	7.77	10	-0.90	9	-1.56
Cancer surgery	5	8.00	4	-0.25	4	-0.50
Benign hematologic disease	16	8.50	14	-0.14	12	-0.33
Malignant hematologic disease	20	8.40	16	-0.25	16	-0.56
Vaccination in relation to surgery						
Prior to surgery	6	8.33	5	-0.80	5	-0.60
< 1 year after surgery	18	7.78	13	+0.25	12	-0.08
> 1 year after surgery	48	8.48	40	-0.70	37	-1.08**
Vaccine						
Pneumovax	55	8.35	45	-0.33	42	-0.60
Pneumovax 23	17	8.12	13	-1.08	12	-1.58
Age						
Less than 40 at surgery	35	8.51	27	-0.59	22	-1.00*
40 or more at surgery	37	8.08	31	-0.42	32	-0.69
Less than 40 at vaccination	31	8.42	25	-0.48	19	-0.84
40 or more at vaccination	41	8.20	33	-0.52	35	-0.80

* $p < 0.01$ (two-sided test); ** $p < 0.005$ (two-sided test).

dextran-coated human erythrocytes with serial twofold dilution of test serum as described [2].

Statistical Methods. The titer values were transformed to the corresponding $^{-2}\log$ values. The statistical analyses were made with conventional two-sided Student's *t* test for correlated pairs; *p* values less than 0.01 were regarded as significant.

Results

Serum samples were collected before vaccination from 72 patients, 6 of whom were vaccinated shortly before elective splenectomy. The remaining 66 patients had been splenectomized on the average 6.25 years prior to vaccination (range 0–30 years). Their average age at splenectomy was 40 years (range 6–72 years). Their diagnoses could be divided into the following groups: trauma, 18 patients; iatrogenic splenic injury (e.g. during ulcer surgery), 13 patients; radical cancer surgery in the upper abdomen, 5 patients; benign hematological diseases (idiopathic thrombocytopenic purpura, spherocytosis etc.), 16 patients, and

malignant hematological diseases (Hodgkin's disease, lymphomas etc.), 20 patients. Thirty-seven of the patients were males, 35 were females. Fourteen and 18 patients did not show up for serum sampling at 6 weeks and 6 months after vaccination, respectively.

The average $^{-2}\log$ DRA titer before vaccination was 8.25 ($n = 72$). The titer was 8.05 ($n = 58$) at 6 weeks (n.s.) and decreased to 7.41 ($n = 54$) in 6 months ($p < 0.01$). The titer values for subgroups are shown in table 1. Significant reduction of prevaccination titer values at 6 months was seen in female patients, trauma patients, patients vaccinated 1 year or longer after surgery and in patients younger than 40 years at splenectomy.

Discussion

The fact that splenectomy increases the susceptibility to severe infections was already suggested early in this century [6], and this was later shown to be true for

children as well as adults [4, 7–8]. Consequently surgeons today try to preserve the spleen in trauma cases or when iatrogenic injury occurs during surgery. Recent studies suggest that reticuloendothelial function is well preserved after splenic repair [9]. For those individuals where splenectomy cannot be avoided or when splenectomy is indicated because of hematological diseases pneumococcal vaccination has been recommended, since overwhelming pneumococcal septicemia is the most frequent type of severe post-splenectomy infection [4].

It would be unfortunate if such vaccination induced an increased risk for these patients to develop severe dextran reactions upon exposure to dextran, especially since the problems with these reactions in other patients lately have been considerably reduced by hapten inhibition [10]. The DRA titers observed in this group of patients were already before vaccination surprisingly high, suggesting that they constitute a group different from the general population in this respect. The distribution of titers of hemagglutinating DRA in individuals with no history of dextran reactions is bimodal, the majority of individuals having titers distributed around a mean of 1:32 ($-2\log = 5$) and approximately 25% having virtually no detectable antibodies to dextran [2]. This type of titer pattern was seen in samples from six different countries studied, although clear differences exist between countries in the percentage of patients with 0 titer or high titers (above 1:2,048, $-2\log = 11$) [11].

Vaccination of the patients studied with polyvalent pneumococcal vaccine induced no rise in the titer of DRA. On the contrary, the initially high titer values were reduced by close to one titer step during the 6-month observation period. Individual subgroups of patients showed minor differences in titer reduction. The titers of patients splenectomized for trauma decreased significantly, even though some immunologically functioning splenic tissue may remain after splenectomy for trauma. It has been suggested that a reduced antipneumococcal antibody production is present both in asplenic but otherwise healthy individuals and in patients who have been subjected to radiation and/or cytostatic therapy [12, 13]. However, in this subgroup the titer values were not noticeably different from the other subgroups before or after vaccination. A titer reduction of approximately the same order was observed after both types of vaccine.

In conclusion, vaccination of asplenic individuals and patients undergoing splenectomy with a polyva-

lent pneumococcal vaccine did not induce the formation of DRA. The patients studied had already prior to vaccination moderately elevated titers of these antibodies and the titer was somewhat reduced during the study period of 6 months. The cause of this is still unexplained.

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