ANNALES
UNIVERSITATIS MARIE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LVIII, N 1, 75 SECTIO D 2003

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Estimation of the efficacy of vaccination against viral hepatitis type B in children with the nephrotic syndrome

Etiopathogenetic factors of the nephrotic syndrome include, among other things, vaccination against different infectious diseases and passive immunization with specific hyperimmune globulins (4, 12). On the other hand, it is well known that the nephrotic syndrome may occur or relapse after different infectious diseases including viral hepatitis type B, especially in cases with persisted HBs antigenemia (1, 5, 12).

Susceptibility of nephrotic children to infection with hepatitis B virus is due to chronic and relapsing course of the nephrotic syndrome, necessity of frequent hospitalization and laboratory studies, frequent transfusions, and disturbances of the immunity system caused by the nephrotic syndrome itself and its treatment (1, 8, 9). In this connection in 1994 we introduced vaccination against viral hepatitis type B in all nephrotic children not immunized in infancy. In addition, we were encouraged to introduce this procedure by the results of the study conducted by Sieniawska et al. (9).

The purpose of the study was to estimate the efficacy of vaccination against viral hepatitis type B in nephrotic children and to estimate the probable cause-effect relationship between the occurrence of the nephrotic syndrome and infectious diseases and vaccinations in children.

MATERIAL AND METHODS

The retrospective study comprised 235 nephrotic children aged 1-14 years hospitalized in the Department of Pediatric Nephrology at University Children Hospital, Lublin, between 1982 and 1997. Vaccine against viral hepatitis type B (Engerix B, Smith-Kline-Beecham) was given to 56 children (33 boys and 23 girls) aged 2-13 years. 49 children received vaccination during the treatment of the nephrotic syndrome. The vaccine was administered to the remaining 7 children during remission. In all children before vaccination the test for the presence of HBs antigen was performed. In children treated with prednisone (Encorton, Polfa) or cyclophosphamide (Endoxan, Asta Medica) the vaccine was given in a twofold dose i.e. 20 microg or 40 microg under the schedule 0 – 1mo – 2mo – 6mo. In children treated with prednisone vaccination was started during the alternate day therapy. If no relapse occurred, the alternate day therapy was followed by tapering of prednisone dose in such a manner that the last dose of the vaccine was given before the end of the treatment. In children treated with cyclophosphamide vaccination was started in the last week of the therapy. In children who achieved remission the vaccine was administered in a stan-

dard dose, i.e. 10 microg or 20 microg under the standard schedule 0 – 1mo – 6mo. In 41 children after the completion of vaccination the titers of antibodies against HBs antigen were measured by immunoenzyme assay. The titer of antibodies against HBs antigen exceeding 10 IU/ml was considered protective.

RESULTS

In 45 of 235 children the nephrotic syndrome was probably induced by different infectious diseases (Tab. 1). In 30 of those children HBs antigenemia was detected. 18 children with HBs antigenemia manifested clinically overt viral hepatitis type B, i.e. the increase in aminotransferases levels and liver enlargement. In 20 children, previously HBs-negative, HBs antigenemia was

Table 1. The percentages of children in whom the first attack or succeeding relapse of the nephrotic syndrome occurred after infectious disease

Infectious diseases	First attack		Succeeding relapse		Total	
	N	%	N	%	N	%
Measles	0	0	3	1.28	3	1.28
Varicella	1	0.42	3	1.28	4	1.71
Rubeola	1	042	1	0.42	2	0.85
Scarlet fever	0	0	2	0.85	2	0.85
Mumps	0	0	2	0.85	2	0.85
Salmonellosis	0	0	1	0.42	1	0.42
Mononucleosis	1	0.42	0	0	1	0.42
HBs antigenemia	10	4.25	20	8.51	30	12.8
Total	13	5.53	32	13.6	45	19.1

detected during the second or succeeding relapses of the nephrotic syndrome. 10 of those children had persistent HBs antigenemia (in 5 children the remission was achieved and the remaining 5 still required therapy) – Table 2. In 15 (5.1%) the nephrotic syndrome was probably due to other infectious diseases. In 7 children the first attack or succeeding relapses of the nephrotic syndrome were induced by measles or DTP vaccination, or by administration of immunoglobulins (Tab. 3). 5 (4 boys and 1 girl) of those 7 children were in prolonged remission (5–13 years). The remaining 2 boys, in whom the first attack and the third relapse of the syndrome were probably induced by measles vaccination, still had the steroid-sensitive frequently relapsing syndrome. The clinical data of 56 children who received vaccination against viral hepatitis type B are presented in Table 4. In 6 (10.7%) of those children the increase in urinary protein excretion was observed and 5 children developed succeeding relapse of the syndrome 7–14 days after the vaccination. Among 25 steroid–sensitive and 31 steroid-dependent or steroid-resistant nephrotic children who received vaccination against viral hepatitis type B 2 (8%) and 4 (12.9%) relapsed, respectively. In 7 children who received vaccination against viral hepatitis type B during remission no complications were observed.

Among the children in whom vaccination-related complications occurred, an increase in urinary protein excretion was observed in two after the first dose of the vaccine and in four the increase in urinary protein excretion was revealed after the second, third and fourth doses of the vaccine. The elevation in urinary protein excretion resolved after the transient increase in prednisone dose. In 55 children the vaccination against viral hepatitis type B was completed. Only in one boy (S.P.) aged 6 years with the steroid-dependent nephrotic syndrome further active

immunization had to be discontinued after the second administration of the vaccine because of heavy proteinuria occurrence. In that boy the first attack of the nephrotic syndrome was probably due to measles vaccination (Tab. 3). Other side effects of vaccination against viral hepatitis type B were not observed.

Table 2. Clinical data of children with the nephrotic syndrome and persistent HBs antigenemia

No	Patient	Sex	Age		No of relapse during which HBs aigenemia was detected	No of relapses	Morphology	Treatment	Present clinical status
			at first attack	at present					
1	Z.D.	F	3.5	13.0	5	6	mesangio-proliferative	prednisone cyclophos-phamide	remission
2	B.K.	M	2.3	5.0	1	1	-	prednisone	remission
3	K.J.	F	2.0	8.6	1	2	mesangio-proliferative	methylpredni-solone prednisone	remission
4	K.Ł.	M	2.1	12.0	3	5	mesangio-proliferative	prednisone cyclophos phamide	remission
5	W.T.	M	3.0	15.3	4	6	mesangio-proliferative	prednisone cyclophos-phamide	still treated
6	P.W.	M	2.4	14.0	7	11	mesangio-proliferative	prednisone cyclophos-phamide	still treated
7	W.K.	M	1.3	15.3	3	18	mesangio-proliferative	prednisone cyclophos-phamide	still treated
8	T.G.	M	5.0	20.0	4	7	minimum change	prednisone cyclophos-phamide	remission
9	Z.K.	M	2.0	9.6	3	7	-	prednisone	still treated
10	P.J.	M	3.0	10.0	6	10	mesangio-proliferative	schedule of Mendoza	still treated

Table3. Children with the first attack or succeeding relapse of the nephrotic syndrome which was probably induced by active and passive immunization against infectious diseases

Syndroma nephroticum	First attack		Succeeding relapses		Total	
	N	%	N	%	N	%
After DTP vaccination	2	0.85	1	0.42	3	1.27
After measles vaccina-tion	2	0.85	1	0.42	3	1.27
After gamma-globulin administration	0	0	1	0.42	1	0.42
Total	4	1.70	3	1.26	7	2.96

Table 4. Clinical data of children with the nephrotic syndrome who received vaccination against viral hepatitis type B

	Children after completion of vaccination		Children with relapse or exacerbation after vaccination completion	
	N	%	N	%
Number of children with the first attack with succeeding relapse	56 20 36	100 35.7 64.3	6 1 5	10.7 5.0 13.9
Boys	33	58.9	2	3.6
Girls	23	41.1	4	7.1
Mean age	5.6		5.4	
Mean lentgh of time	3.6		3.0	
Mean number of relpses	4.0		3.4	
Type: steroid-sensitive steroid-dependent steroid-resistant	25 29 2	44.6 51.8 3.6	2 3 1	8.0 10.3 50.0
Therapy: prednisone 0.5 – 2 mg/kg mc./48h remission	49 7	87.5 12.5	6 0	10.7 0

In 41 of 56 children who received vaccination against viral hepatitis type B the titers of anti-HBs antigen antibodies were measured. Protective titers were achieved in 39 (95.1%) children. In 32 (78%) of those children the titers of anti-HBs antigen antibodies exceeded 100 IU/ml despite different periods of time between the completion of vaccination and titer measurement (Fig.1). The titers of anti-HBs antigen antibodies below the protective level were observed in two boys. One of them aged 12 years had diffuse mesangial proliferation, and the second one was presented with the steroid-dependent nephrotic syndrome. Among 6 children with titers of anti-HBs antigen antibodies below 60 IU/ml one girl had the steroid-sensitive nephrotic syndrome, two boys had the frequently relapsing nephrotic syndrome and three children were after cyclophosphamide therapy (two of them had diffuse mesangial proliferation). In all the children who achieved remission followed by vaccination against viral hepatitis type B protective titers of anti-HBs antigen antibodies were attained.

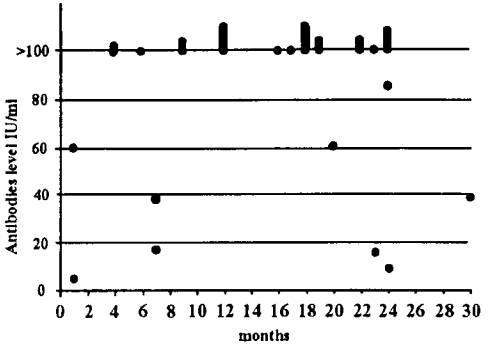

Fig. 1. The titers of anti-HBs antigen antibodies in children with nephritic syndrome with regard to period between vaccination completion and titer measurement

DISCUSSION

Hbs antigenemia was detected in 30 (12.8%) nephrotic children. 10 of those children had persistent HBs antigenemia. Only 5 children with persistent HBs antigenemia achieved remission. The remaining 5 children with persistent HBs antigenemia still required therapy because of succeeding relapses of the nephrotic syndrome. The prognosis in those children was uncertain. Exceptionally high percentage of HBs antigenemia in nephrotic children confirms the high susceptibility of those children to infection with hepatitis B virus. It is highly probable that in 10 (4.3%) children with HBs antigenemia detected during the first attack of the nephrotic syndrome, the infection with hepatitis B virus induced the occurrence of the syndrome. In the remaining 20 children Hbs antigenemia was revealed during succeeding relapses of the nephrotic syndrome. Infection with hepatitis B virus in those children seems to be the result of immune system disturbances on the one hand (8), and on the other, the effect of higher exposure to hepatitis B virus on the other.

Usefulness of vaccinations against viral hepatitis type B in children and adult at high risk of infection is nowadays undoubted (3, 6, 9, 10). In children with the nephrotic syndrome the problem when to start vaccination is controversial. Undoubtedly, the most optimum period is remission after completion of treatment with prednisone or alkylating agent. However, the risk of infection during the therapy should be taken into account. If it occurs it may have unfavorable influence on the clinical course of the syndrome (1, 11). In 1994 we introduced vaccinations against viral hepatitis type B in all nephrotic children not immunized in infancy. The first dose of the vaccine is administered when clinical symptoms and biochemical abnormalities subside during alternate day therapy with prednisone or during the last week of therapy with cyclophosphamide.

In 43 of 49 children who received the first dose or the vaccine during alternate day therapy with prednisone no complications were observed. However, in 6 children exacerbation of the syndrome occurred 7–14 days after vaccination. The exacerbation of the syndrome was probably induced by vaccination and resolved after a transient increase in prednisone dose. Because spontaneous exacerbation of the nephrotic syndrome during the therapy may occur, it is impossible to state most certainly that there was a cause-effect relationship between vaccination and exacerbation of the syndrome in those children. However, there were no other detectable factors which might induce exacerbation.

In 41 of 49 children who received vaccination against viral hepatitis type B the titers of anti-HBs antigen antibodies were measured. In 39 (95.1%) of those children the titers of antibodies against HBs antigen exceeded the minimum protective level, i.e 10 IU/ml. In 2 children titers of antibodies against HBs antigen failed to achieve the minimum protective level. Those 2 children and children in whom the titers of antibodies against HBs antigen did not exceed 60 IU/ml had the steroid-dependent or steroid-resistant and/or frequent relapsing nephrotic syndrome. Those children required a prolonged therapy with prednisone or cyclophosphamide. The relationship between intensive therapy and failure to achieve the protective antibodies titer after vaccination was also observed by other authors (2,6,10). In such children it is necessary to measure antibodies titers once a year. In case of low antibodies titer the booster dose of the vaccine should be given.

CONCLUSIONS

1. Both active immunization and infectious diseases may induce the nephrotic syndrome in children. Despite this, in children with the nephrotic syndrome vaccination against viral hepatitis type B is recommended since it influences favorably the further clinical course of the syndrome by protection

against the disease. In our study none of the children who received vaccination developed viral hepatitis type B.

2. Taking into account the high percentage of the infections with hepatitis B virus after the second or succeeding relapses of the nephrotic syndrome, vaccination against the disease should be started during prednisone alternate day therapy of the first attack of the syndrome.

3. The high percentage of nephrotic children with protective titers of anti-HBs antigen antibodies after vaccination confirms the usefulness of the recommended dose of the vaccine and vaccination schedule.

4. In children who achieved remission the dose of the vaccine and the vaccination schedule do not differ from those in healthy children.

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SUMMARY

The purpose of the study was to estimate the efficacy of vaccination against viral hepatitis type B in children with the nephrotic syndrome and to estimate the probable cause-effect relationship between the occurence of the nephrotic syndrome and infectious diseases and vaccination in children. The retrospective study comprised 235 nephrotic children aged 1-14 years hospitalized in the Depertment of Pediatric Nephrology at University Children Hospital, Lublin, between 1982 and 1997. 56 nephrotic children aged 2–13 years received vaccination against viral hepatitis type B. In 49 children the vaccine was administered during the treatment of the nephrotic syndrome and in the remaining 7 children – after completion of the therapy.

Retrospective analysis revealed the presence of infection with hepatitis B virus in 30 (12.8%) nephrotic children. In 20 of those children the presence of infection with hepatitis B virus was detected during the second and succeeding relapses of the syndrome. In 15 (5.1%) children the nephrotic syndrome was probably induced by other infectious diseases and in 7 children the nephrotic syndrome developed as a result of active immunization. Among 56 children who received vaccination against viral hepatitis type B in 6 (10.7%) the increase of urinary protein excretion was observed and 5 developed a succeeding relapse of the syndrome. In 41 of 56 children who received vaccination against viral hepatitis type B the titers of anti-HBs antigen antibodies were measured. The protective titer of anti-HBs antigen antibodies was detected in 39 (95.1%) nephrotic children. It is well known that both active immunization and infectious diseases may induce the nephrotic syndrome. Despite this, vaccination against viral hepatitis type B in nephrotic children is highly recommended, since it influences favorably the further clinical course of the syndrome by the protection of the disease. In our study, none of the nephrotic children who received vaccination developed viral hepatitis type B.

Ocena skuteczności szczepień ochronnych przeciw wirusowemu zapaleniu wątroby typu B u dzieci z zespołem nerczycowym

Celem badań była ocena skuteczności szczepień przeciw wirusowemu zapaleniu wątroby typu B u dzieci z zespołem nerczycowym oraz prawdopodobnych związków przyczynowo-skutkowych między występowaniem zespołu nerczycowego a chorobami zakaźnym i szczepieniami ochronnymi. Badaniem retrospektywnym objęto 235 dzieci z zespołem nerczycowym w wieku 1–14 lat, hospitalizowanych w latach 1982-1997 w Klinice Pediatrii i Nefrologii. Szczepienia przeciw wirusowemu zapaleniu wątroby typu B przeprowadzono u 56 dzieci w wieku od 2 do 13 lat, w tym u 49 dzieci szczepienia wykonano w okresie leczenia zespołu nerczycowego, a u siedmiorga pozostałych po zakończeniu leczenia. Analiza retrospektywna wykazała obecność zakażenia wirusem zapalenia wątroby typu B u 30 (12,8%) dzieci z zespołem nerczycowym, z tego u 20 zakażenie stwierdzono w okresie drugiego lub kolejnych rzutów choroby. U 15 (5,1%) dzieci zespół nerczycowy był prawdopodobnie wywołany przez inne choroby zakaźne, zaś u 7 dzieci zespół nerczycowy indukowany był przez szczepienia ochronne. Wśród 56 dzieci zaszczepionych przeciwko HBV u 6 (10,7%) obserwowano narastanie białkomoczu aż do wystąpienia pełnego rzutu zespołu nerczycowego u 5 z nich. U 41 dzieci, z 56 poddanych szczepieniu przeciw wirusowemu zapaleniu wątroby typu B, oznaczono poziom przeciwciał przeciwko antygenowi HBs. Miano ochronne przeciwciał powyżej 10 IU/ml stwierdzono u 39 (95,1%) dzieci. Wiadomo, iż zarówno szczepienia ochronne, jak i choroby zakaźne mogą indukować wystąpienie zespołu nerczycowego. Pomimo to szczepienie przeciwko wirusowemu zapaleniu wątroby typu B u dzieci z zespołem nerczycowym jest zalecane, ponieważ wywiera korzystny wpływ na kliniczny przebieg zespołu, chroniąc przed wystąpieniem choroby. W naszych badaniach u żadnego dziecka z zespołem nerczycowym nie obserwowano zakażenia wirusem zapalenia wątroby typu B.