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Alloimmune neonatal neutropenia: Clinical observations and therapeutic consequences

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Alloimmune neonatal neutropenia is a rare condition, it must be distinguished from hereditary forms of neutropenia and acquired neutropenia accompanying sepsis.

In a family with four affected newborns, the degree of the disease became more and more severe from the first child to the third child. The third child died of sepsis. After birth of the third child, specific antibodies (anti-NA 1) reacting with the neutrophils originating from the father and the first two children were detected in the mother's serum. No neutrophils were detectable in the fourth child immediately after birth. In this child falling concentrations of diaplacentally transferred antibodies could be demonstrated over 8 weeks after birth. Neutrophil counts returned to normal as the antibodies disappeared. In this newborn, infection could be prevented by the use of a germ-free environment and antimicrobial prophylaxis. The antibody titres could only be lowered by repeated exchange transfusions with Na 1-free blood. White blood cell transfusion only resulted in a short transient effect on neutropenia.

Familial occurrence of neonatal neutropenia is rare. The best-known condition is infantile hereditary agranulocytosis (Kostmann syndrome), transmitted as an autosomal recessive trait, readily distinguishable from other forms of neutropenia by its clinical course and haematological findings. The prognosis of this disorder is grave, most cases die of bacterial infection during early childhood, only few patients survive to adulthood. In peripheral blood persistent granulocytopenia below 0.3 G/1, and an increased number of monocytes and eosinophils can be observed. The bone-marrow is rather characteristic, exhibiting inhibited maturation at the level of promyelocytes and myelocytes.

Benign cyclic neutropenia is characterised by periods of mild febrile infection accompanied by granulocytopenia in peripheral and bone-marrow smears. Between the attacks the patients have normal neutrophil counts. The condition is inherited as an autosomal dominant trait, its appearance is not restricted to early infancy. Familial neutropenia with hypergammaglobulinaemia is also transmitted in an autosomal dominant way with a mild manifestation from the first year of life.

Myelocathexis or chronic agranulocytosis can be distinguished from the above mentioned forms by the bone-marrow finding characterized by inhibited release; accumulation of hypersegmented neutrophile granulocytes can be observed.

Constitutional familial leucocytopenia with partial Pelger—Huet anomaly [7a], also termed myelolymphatic insufficiency, is an X-linked recessive condition, the clinically healthy carriers exhibit nuclear anomalies similar to the Pelger anomaly in their neutrophils.

In addition to these hereditary forms of neutropenia immune neutropenia also occurs, either as alloimmune neonatal neutropenia, autoimmune neutropenia, or as chronic benign neutropenia. Alloimmune neonatal neutropenia is less known to paediatricians and physicians employed in the blood transfusion service; still, it needs extraordinary clinical and laboratory efforts. Thus, description of our own experience and comparison with published findings may appear useful.

Report of Cases

B.M., a woman in the seventh week of her fifth pregnancy, attended a genetic counselling service because her three children had been affected by local and/or septic infection accompanied by granulopenia during the neonatal period. The disease was progressively severe in the children, in fact, the third child died of an infection. In addition, she had a pregnancy aborted in fear of an affected child. She reported that during three of her four pregnancies she had suffered of purulent infections of her toes in the first months and that during the fifth to tenth weeks of her actual pregnancy she had an abscess in the mental region; at no other times had she had suppurative skin disorders.

1.1. Patient M.M. The first child developed purulent rhinitis on his fifth day of life; loss of appetite, vomiting, fever of 39°C, facial pyoderma, paronychia on an index finger and purulent conjunctivitis appeared on the seventeenth day of life. Cultures revealed Staphylococcus aureus. The condition abated by the 28th day of life on treatment with ampicillin, oxacillin and gentamicin. Blood taken on the 18th day of life showed haemoglobin: 12.1 mmol/l; leucocyte count: 7.6 G/l; eosinophils: 0.05; rods: 0.02; bands: 0.01; segmented: 0.02; lymphocytes: 0.86; monocytes: 0.02; large lymphocytes: 0.02. Checking at nine months of age and later revealed normal leucocyte and neutrophil counts.

1.2. Patient D.M. Fever of 38.5°C and lymphadenitis in the left axillary region appeared on the fifth day of life. In spite of ampicillin, oxacillin and polymyxin B therapy, abscess formation necessitated surgery on the tenth day. Bacterial culture revealed Pseudomonas aeruginosa. On the twelfth day of life retroauricular pyoderma, abdominal distension and liver and spleen enlargement appeared. Thoracic X-ray revealed disseminated bronchopneumonia. During the subsequent two weeks a life-threatening condition developed. As a consequence of parenteral nutrition, white blood cell transfusions and antibiotic

treatment, gradual improvement of the septic condition supervened.

Up to the 13th day of life 1—2% segmented neutrophile granulocytes, thereafter young granulocytes appeared, from the 19th day of life segmented granulocytes could also be observed (Table I). Poor cellularity in the bone-marrow, normal B/T ratio among the lymphocytes. Immune globulins, measured on the eighth day of life: IgA: less than 0.01 g/l; IgM: 0.076 g/l; IgG: 1.02 g/l.

1.3. Artificial abortion because of fear of another affected child.

1.4. Patient Ch.M. From the third day of life fever between 38.0 and 39.5°C, from the 6th day of life marked abdominal distension. An abdominal X-ray revealed only distended intestines. Moderate hepatosplenomegaly. Small quantities of mucous faeces. Pseudomonas aeruginosa, Enterococcus and Escherichia coli were cultured from the stools. Blood culture of bacteria and fungi was negative. Enterocolitis was anticipated and parenteral feeding plus antibiotic therapy was introduced. The patient's condition deteriorated. In the lower right quadrant of the abdomen a tender resistance of tomato size appeared in the distended abdomen, the presence of an intraabdominal abscess and diffuse peritonitis was suspected. Oedema, severe oliguria, hyponatraemia, increased direct bilirubin level (total: 188 μmol/l, direct: 154 μmol/l) and serum transaminase activity, thrombocytopenia and an exanthem complicated the picture. The child died of bronchopneumonia on the 45th day of life.

Necropsy revealed chronic fibroplastic colitis with perforation of the transverse colon, chronic diffuse peritonitis, abscess in the right lower quadrant, bronchopneumonia, pleural and pericardial effusion, toxic hepatosis and lipaemic nephrosis.

TABLE I

Haematological findings of Patient D. M.

	Day										
	6	8	12	13	14	15	19	20	22	24	30
Haemoglobin, mmol/l	9.5	10.6	9.8	10.4	10.4	10.0	9.0	10.2	7.0	6.6	6.8
Packed cell volume	0.43	0.50	0.51								
Leucocytes, G/l	5.2	10.0	4.8	11.3	10.8	18.7	35.8	24.8	8.7	5.2	6.4
basophils	—	—	—	—	—	—	—	—	—	—	—
eosinophils	7	7	11	—	6	5	—	3	—	—	5
promyelocytes	4	—	—	3	10	2	1	3	—	—	—
myelocytes	1	—	—	10	9	3	22	24	—	3	4
young	—	—	—	1	33	6	24	5	—	1	1
rods	—	—	3	—	4	4	19	16	24	1	2
segmented	1	1	2	—	—	—	11	16	32	26	21
lymphocytes	36	57	72	72	29	41	14	26	44	58	58
monocytes	44	34	12	7	4	6	9	8	—	10	9
Platelets, G/l	245	65	26		175		230	400	85		43
Reticulocytes, per mil			10						4		

TABLE II

Haematological findings of Patient Ch. M. I.

	Day								
	6	8	10	15	18	23	28	34	41
Haemoglobin mmol/l	9.3	8.8	7.6	8.7	8.8	6.3	5.7	6.4	5.8
Packed cell volume	0.48	0.46	0.40	0.46	0.46	0.32	0.31	0.40	0.30
Leucocytes, G/l	4.7	5.2	5.3	4.7	4.0	22.0	36.0	41.0	14.8
promyelocytes	—		7	2	2	6	1	—	—
myelocytes	3		13	2	3	2	1	—	—
basophils	—		—	—	—	—	1	1	—
eosinophils	1		4	6	2	2	3	1	1
young	3		21	12	11	9	—	—	1
rods	10		5	37	51	17	10	27	31
segmented	3		—	23	20	49	52	55	28
lymphocytes	23		40	14	12	11	30	14	35
monocytes	4		4	1	—	2	2	—	4
lymphocytes	3		6						
Platelets, G/l	63	17	80	8	5	30	75	33	40
Reticulocytes, per mil	8		1		6	19	4	11	

Laboratory findings. During the first 14 days of life normal leucocyte counts comprising only 3% segmented granulocytes, 16 and 46% immature granulocytes were found. The granulocyte count increased from the third week of life to 23%, with leucocytosis during the 4th week exceeding 40 G/l, with 50% granulocytes and a shift to the left. From the second week of life the thrombocyte count was between 8 and 75 G/l (Table II). C-reactive protein (8th day): 0.012 g/l, IgA: undetectable, IgM: 0.4 g/l, IgG: 1.120 g/l, rubella antibodies: 1 : 128, CMV (complement binding reaction): negative, toxoplasma antibody: 1 : 16, HB_2Ag: negative.

During and after the fifth pregnancy, clinical, haematological and immunological studies were carried out in the mother and her child and the effect of prophylactic and therapeutic measures was studied.

METHODS

Immunological investigations were carried out monthly in the mother and daily respectively weekly in the newborn baby. Maternal serum was reacted with cell suspensions of the close relatives, with cells of selected and unselected blood donors with known HLA-A, -B, -C and NA 1, NA 2 and NB 1 antigens. The methods used were leucocyte agglutination test of Rood et al [22], indirect immunofluorescence test of Verheugt et al [28] and the lymphocyte toxicity test of Blaschke et al [2].

Blood for exchange transfusion and white blood cell transfusion was selected from donors with blood group 0 d, exhibiting no leucocyte agglutination with the maternal serum. In all available family members blood groups were determined, HLA typing and leucocyte agglutination tests were carried out.

Prior to the birth of the newborn a sterile, germfree environment was prepared according to the usual criteria.

Labour occurred in Dresden, the first steps were performed in the Department of Paediatrics in Dresden (the first two exchange transfusions). Then the child was

transferred to the Second Department of Paediatrics in Berlin-Buch, where the facilities seemed to be more appropriate.

Results

Tests for maternal antibodies. The leucocyte agglutination test revealed agglutinating antibodies against neutrophil granulocytes with a specificity for NA 1, in a titre of 1 : 16 during the whole course of pregnancy. Also, the indirect immunofluorescence test resulted in a positive reaction whenever the test cells carried the NA 1 antigen.

In addition, an antibody specific for HLA—B 17 (57 + 58) was found in a titre of 1 : 2. This antibody could be demonstrated from the eighth month of pregnancy only in undiluted serum; the antibody reacted in the indirect Coombs test on erythrocytes as anti-Bg(b). The immunological findings were described in detail by Leverenz et al [18].

Studies of the family members. The maternal antibody specific for granulocytes reacted only with granulocytes of her children, her husband and his relatives, while with none of her own family members. HLA-typing demonstrated in the first child no haplotype against which the maternal antibody specific for HLA-B 17 (57 + 58) was active although this child had exhibited neonatal neutropenia.

Findings in the newborn. No antibodies could be demonstrated by the lymphocyte toxicity test in cord blood and retroplacental blood. On the other hand, these sera contained the same titre of the granulocyte specific antibody as the maternal serum. The course of the titre is shown in Figure 1.

Delivery. Vaginal irrigations were performed prior to the date of delivery planned for the 38th week of pregnancy. Delivery itself and the first manipulations on the newborn were carried out under germ-free sterile conditions. The newborn baby had a normal appearance. The haematological findings obtained immediately after birth pointed to a complete absence of immature and mature neutrophile granulocytes. The absolute and relative number of eosinophils and monocytes was increased.

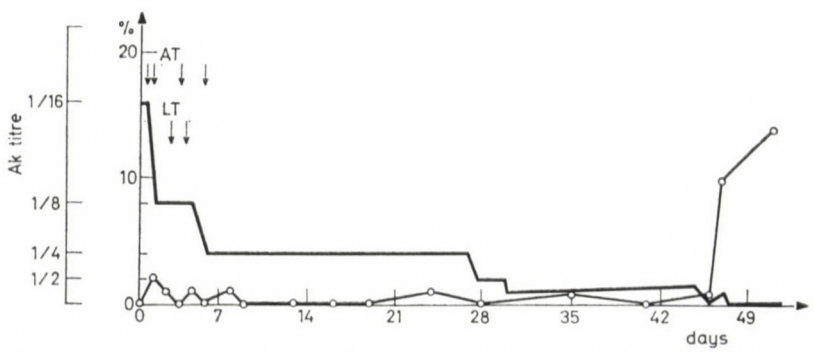

Fig 1. Reactions of neutrophil specific antibodies in the leucocyte agglutination test. ET: Exchange transfusion; LT: Leucocyte transfusion

Care of the newborn. The baby was kept in a sterilized incubator in an isolated room. To reduce the number of enteral germs the newborn was treated daily with 10 mg/kg oral polymyxin B, 150000 IU oral nystatin and 100 mg/kg/day intravenous cephoxitin from the first hour of life. The baby was fed deep-frozen colostrum, then breastmilk originating from a woman who expressed her milk under germ-free conditions. There were no granulocyte specific antibodies in the colostrum of the child's mother but HLA-B 17 antibodies were present in a titre of 1 : 4.

Exchange transfusions using 200 ml/kg heparinized fresh blood (a mixture of packed red cells 0 d and AB d plasma, each free of NA 1 and HLA-B 17 (57 + 58) were started three and 24 hours after birth respectively. One hour after completion of the first exchange transfusion only 2% neutrophile granulocytes could be detected and even four hours after the second exchange transfusion as little as 10% were found. Therefore two additional exchange transfusions were given using fresh blood free of NA 1 and HLA-B 17. Still, the neutropenia persisted unchanged (Table III).

There was, however, a recognizable effect of the exchange transfusions on the antibodies. At the end of each exchange transfusion the antibodies gave only a weak reaction but 24 hours later there was a marked rebound each time. The net effect of the four exchange transfusions was a fall in the titre by two dilutions.

On the third day of life 20 ml/kg leucocyte concentrate, containing $6.8 \cdot 10^9$ leucocytes, 58% neutrophile

TABLE III

The effect of exchange transfusions on leucocyte counts and antibody levels

	Day of life							
	1		2		4		6	
			before	after	before	after	before	after
	immediately after birth	after 1st exchange transfusion	second exchange transfusion		third exchange transfusion		fourth exchange transfusion	
Leucocytes, G/l	6.8	3.6	4.7	2.9	5.5	5.3	13.0	7.2
Blood smear								
myeloblasts	—	0.03	—	0.01	—	—	—	—
promyelocytes	—	0.01	—	0.01	—	—	—	—
myelocytes	0.04	0.02	0.03	0.03	0.01	0.06	0.02	—
basophils	—	—	—	—	—	—	—	—
eosinophils	0.11	0.12	0.05	0.06	0.32	0.17	0.07	0.04
young	0.02	0.01	0.03	0.01	—	0.02	—	0.01
rods	—	—	0.03	0.01	0.01	0.01	—	0.01
segmented	—	0.02	0.04	0.10	0.04	—	0.01	0.02
monocytes	0.59	0.46	0.60	0.40	0.32	0.23	0.31	0.23
lymphocytes	0.24	0.33	0.23	0.37	0.28	0.46	0.50	0.54
large lymphocytes	—	—			0.02	0.05	0.09	0.15
Anti-NA 1 titre	1 : 16	—	1 : 16	—	1 : 8	1 : 4	1 : 8	1 : 4

granulocytes, blood group 0 d, free of NA 1 and HLA-B 17, was transfused over three hours. Unequivocal clinical side-effects were not observed. Obstinate nausea occurred during the transfusion of leucocytes, this was ascribed to oral glucose administration. Oscillations in the respiratory rate accompanied by transient irregularity were related to the sleep/wakeness rhythm. A circumscript skin rash consisting of small patches on the right thorax appeared but rapidly subsided. Two hours after the leucocyte transfusion a marked increase in the neutrophil count was observed but it returned to the previous level by 16 hours after transfusion (Table IV). Fifteen hours after the third exchange transfusion, 36 hours after the first transfusion of leucocytes, a second dose of leucocyte concentrate was applied, 60 ml containing $6.1 \cdot 10^9$ leucocytes with 73% neutrophile granulocytes were transfused. In contrast to the first leucocyte transfusion, the effect of the second one on the blood smear was moderate. There were no marked side-effects during and after this second leucocyte transfusion. Also this time, however, the newborn had nausea, transient irregularities in respiratory rate and 14 hours after transfusion a transient exanthem consisting of large patches appeared on the trunk and some areas of the extremities. Oedema supervened on the sixth to seventh day. Changing skin colour, transient alterations in the respiratory rate were seen. Auscultation over the thorax was normal, a chest X-ray revealed discrete streak shadows in the right lung. Since pneumonia could not be excluded, the therapy initiated shortly after birth was supplemented by Gamma-M concentrate. The above mentioned

TABLE IV

The effect of leucocyte concentrate transfusions on the blood picture

		I					II			
		Before	2	10	16	28	Before	4	12	27
		hours after transfusion					hours after transfusion			
Leucocytes, G/l	Gpt/1	4.0	6.8	4.6	5.5	5.3	see ←	11.1	13	7.2
Blood smear										
myeloblasts		—	—	—	—	—		2	—	—
promyelocytes		—	—	—	—	—		—	—	—
myelocytes		6	2	3	1	6		—	2	—
basophils		—	—	—	—	—		—	—	—
eosinophils		31	9	20	32	17		7	7	4
young		2	1	—	—	2		1	—	1
rods		3	2	2	1	1		7	—	1
segmented		1	32	12	4	—		17	1	2
monocytes		40	19	40	32	23		22	31	23
lymphocytes		17	35	21	28	46		33	50	54
large lymphocytes				2	2	5		11	9	15
Platelets, G/l	Gpt/1	150	184	136	183	92		71	220	50

phenomena were observed during three days, during this period the newborn gained weight in a satisfactory manner. After 6 days there were no pulmonary abnormalities.

During the third week of life high doses of human gamma-globulin 5% made by Institute of Vaccines, Dresden, 1.2 g i.v. on five consecutive days, was applied in order to increase the peripheral neutrophil count since daily checking had revealed 0—1% neutrophile granulocytes and the tests for the maternal antibody were still positive. There was no favourable effect. Similarly, 15 mg of prednisolone divided into two doses, given on the 25th and 26th day failed to increase the neutrophil count. At this time all antimicrobial drugs were stopped. The child gained weight and exhibited no symptoms of an eventual infection. These encouraging events prompted us to continue only the germfree environment.

In the 8th week of life the antibodies could only be demonstrated in undilated serum and they disappeared by the ninth week of life. A corresponding increase in the neutrophil count soon ensued and the child could be discharged during the tenth week of life. Its blood smear was regularly checked, no abnormalities were found up to the eighth month of life, each time a normal leucocyte count and a normal distribution were observed.

The bone-marrow was examined twice. A tibial biopsy was carried out on the eighth day of life, it showed hypoplastic bone-marrow with inhibited maturation of the neutrophile granulocytes. A second bone-marrow specimen was obtained again by tibial punction during the 9th week of life, this time a specimen with high cellularity and exhibiting satisfactory regeneration of granulo- and thrombocytopoiesis was obtained.

Discussion

There is no doubt that the neonatal neutropenia in all of four siblings was caused by an immunological process. Similar observations were published by several authors [8, 17, 19, 24, 25]. In all described families maternal antibodies reacting with the granulocytes of the newborn and the father, respectively, were demonstrated. While the titre in the mother persisted after delivery, a continuous, gradual decrease of the transplacentally transferred antibodies was seen in the children. A concomitant increase in the neutrophil count was then observed, accompanied by healing of the initial local and systemic infections. In analogy to the incompatibilities of the erythrocyte antigen systems, Hitzig and Gitzelmann [8] proposed the term morbus leucolyticus neonati.

Elucidation of the leucocyte antigen-antibody systems was furnished by Lalezari et al (9—16), later on by Verheugt et al [28] and Claas et al. [6]. The earlier clinical observations were then checked in retrospection by new immunological methods, and by now all cases have been fully clarified and the disease is now termed

as isoimmune neonatal neutropenia, as proposed by Lalezari.

As to the clinical picture, a review of 19 cases [15] showed that only four affected babies were first-born, all other patients came from multiparous pregnancies. Also primiparous mothers without any blood transfusion in their history had affected children. A progressively increasing degree of severity, as seen in our cases, has not been firmly established.

The clinical symptoms are variable, in most cases there are febrile local and/or systemic infections during the first week of life. Pyoderma, abscess formation, omphalitis, otitis media, bronchopneumonia, urinary tract infection and sepsis were described but there were asymptomatic cases as well. 2 out of 19 evaluated children died during the second and third week of life, one of pneumonia, the other of sepsis [15].

The fatal outcome of the third child in the family observed by us on the 45th day after birth, at a time when the leucocyte count was already normal, can still be ascribed to the underlying immune process since the disease manifested early and was only prolonged by our treatment.

In alloimmune neonatal neutropenia the spectrum of pathogenic agents comprises mostly staphylococci but also beta-haemolysing streptococci and Escherichia coli. In our own case staphylococcus was demonstrated once and Pseudomonas aeruginosa twice.

The most characteristic haematological finding was a lack or very low number of neutrophile granulocytes, the immature forms included. The finding is present immediately after birth like in the third child of our family. The duration of neutropenia varies from 2 to 15 weeks. At the summit of the local or systemic infections, immature neutrophile granulocytes may appear, further increasing the already high leucocyte count caused by elevation of the monocyte and eosinophile granulocyte counts. All mothers have normal leucocyte counts during pregnancy and after delivery.

The bone-marrow findings are not unequivocal. Increased cellularity with a marked shift to the left in granulopoiesis may prevail; promyelocytes and metamyelocytes dominate while rods and segmented forms are hardly seen. On the other hand, bone-marrow hypoplasia may also be found as was the case in our patient.

It is difficult to evaluate the effect of therapeutic measures described in the literature. In certain cases expectative behaviour and a germ-free environment may suffice since there have been asymptomatic cases. The consequent onset of infections of progressive severity during the first week of life and the fatal outcome in the third child of the family made us suppose that in addition to germ-free care antibiotic and antimycotic treatment supplemented by repeated exchange transfusions was mandatory in the last child of the family.

Our attempt to restitute the neutrophil count by prophylactic leucocyte transfusions has failed. The effect

was so short that the preparation should have been given every day or every second day on a theoretical basis. Since a mean duration of seven weeks can be expected for the neutropenia, an extremely large number of leucocyte transfusions should be applied. This procedure, however, would involve an unjustifiable high risk of immunological complications and other undesirable side-effects. We are thus for a therapeutic indication of leucocyte transfusions. Even incipient local or systemic infection would be such an indication. No side-effects directly ascribable to the leucocyte transfusion were observed, it could, however, not be excluded that the alterations in the respiration rate and the chest X-ray findings were caused by transient pulmonary sludging evoked by the leucocyte transfusion. The course of the disease was not typical for pneumonia. The pulmonary abnormality appeared four days after initiation of the prophylactic antibiotic treatment and all respiratory symptoms and findings resolved without changes. The same holds for the transitory skin phenomena.

By analogy to the alloimmune haemolytic disease of the newborn we expected a drastic fall in the antibody levels after the early exchange transfusion with NA 1 free blood. In spite of the fact that hardly any quantity of antibody was found immediately after exchange transfusion, a marked rebound was observed by the end of the first day following the exchange transfusion. Still, we succeeded in reducing the titre to a level two dilutions lower by four consecutive exchange transfusions. This kind of treatment had no measurable effect on the neutrophil count. Further exchange transfusions might have additionally lowered the antibody level but we felt that for the increasing risk of repeated invasive methods this was not justified. Unfortunately, there are hardly any reports on experience with exchange transfusions carried out in alloimmune neonatal neutropenia, although most case reports mention the necessity and effectiveness of the procedure [7].

Since the exchange transfusions and the leucocyte transfusions have failed, we attribute a major role to germ-free care in the treatment of this transitory but severe disorder.

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