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ORIGINAL ARTICLE

Severe Transitory Neonatal Neutropenia Associated with Maternal Autoimmune or Idiopathic Neutropenia

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Abstract

Purpose Neonatal immune neutropenia is observed in rare cases in newborns from mothers with idiopathic or autoimmune neutropenia, secondary to passive transfer of maternal granulocyte auto-antibodies.

Methods We performed a literature review and report four supplementary cases from the French registry of neutropenia.

Results Only 14 cases (11 mothers, 14 newborns) have been reported. Granulocyte aggregation (GAT) and granulocyte indirect immunofluorescence test (GIFT) are the recommended laboratory procedures for antibody detection. Monoclonal antibody-specific immobilization of granulocyte antigens (MAIGA)-confirmed antibody specificity.

Antibody detection in newborns is not generally possible owing to extreme neutropenia. In half of the cases autoantibodies against neutrophils (AAN) were positive in maternal sera (7 out of 11). In some newborns tested, IgG^+ AAN were also positive, with disappearance in parallel of spontaneous neutrophil count improvement. No correlation between maternal type of AAN and titer and neonatal neutropenia can be established. Neutropenia resolved spontaneously between 2 weeks and 4 months. Infections in newborns were observed in 43% of cases, with no deaths reported. Granulocyte colony-stimulating factor (G-CSF) was administered to some newborns (5 out of 14) in the case of infections. Low-dose G-CSF administered to childbearing women during pregnancy could be proposed to prevent neutropenia in newborns.

Conclusions From the few cases reported so far it is impossible to draw any conclusions regarding frequency, risk factors, and outcome, but the overall prognosis for newborns seems good. Because it can be associated with potentially severe neonatal infections, autoimmune neutropenia in childbearing mothers should be closely monitored in collaboration with gynecologists and pediatricians.

Keywords Neonatal neutropenia · Autoimmune neutropenia · Transitory neutropenia · Anti-neutrophil antibody

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Introduction

Autoimmune neutropenia in infancy is rare, with an estimated incidence of 1 out of 100,000 children [1]. The median age at diagnosis is 7–9 months and it is exceptional at less than 1 month [2, 3]. A different setting is alloimmune neutropenia; it resolves spontaneously weeks or months after birth. Alloimmune neutropenia is relatively frequent, estimated in 1 out of 6,000 newborns owing to feto-maternal granulocyte mismatch.

In rare cases, neonatal immune neutropenia is observed in newborns from mother with idiopathic or autoimmune neutropenia. Among 108 adult patients enrolled in the French Severe Chronic Neutropenia Registry, a transient profound asymptomatic neutropenia was detected at birth in four infants [4]. It has been documented in some cases to be related to the

passive transfer of maternal granulocyte auto-antibodies. Less than 10 cases have been reported [5–9]. This is the rarest form of immune neutropenia of early infancy. The severity and duration of neutropenia are currently unknown.

We performed a narrative literature review on MEDLINE (National Library of Medicine, Bethesda, MD). The keywords used for the search were "neonatal neutropenia." Clinical articles in French or English published since 1955 were considered.

We report four supplementary cases of this rare cause of newborn neutropenia from the French registry of neutropenia [4].

Case reports

Case 1

A 32-year-old woman was known to have idiopathic neutropenia (neutrophils <0.5 × 10 G/L) and celiac disease since the age of 19. Several tests for anti-neutrophil antibodies were negative (granulocyte agglutination test [GAT] for the detection of antibodies reactive with neutrophil antigen HNA-1 and HNA-2 and flow cytometry) and *ELANE* gene (neutrophil elastase gene) sequencing did not identify pathogenic variants. Antinuclear antibodies were negative. Because she presented with spondylodiscitis (*Staphylococcus aureus*) and recurrent skin abscesses at the age of 21, she received granulocyte colony-stimulating factor (G-CSF) until she was 27 years of age. She had a first uncomplicated pregnancy at 29 years. At 32 years, she gave birth to a boy by spontaneous vaginal delivery at 35 weeks' gestation. Her neutrophil count during pregnancy was always above 1.5 G/L, but declined at 0.45 G/L after delivery. A systematic blood cell count of the child revealed severe neutropenia (< 0.1 G/L) at birth, which resolved at 2 weeks without infectious complications.

Case 2

A 30-year-old woman was known to have idiopathic neutropenia since the age of 10, with fluctuating neutrophil count between 0.2 G/L and normal values. *ELANE* gene sequencing did not identify pathogenic variants and anti-neutrophil antibodies were negative (GAT and modified monoclonal antibody immobilization of granulocyte antigens [MAIGA]). Granulocyte indirect immunofluorescence test (GIFT) showed IgG positivity but IgM negativity. GIFT was concluded to be negative by biologists). She was treated with long-term G-CSF. During her second pregnancy (she had an abortion for the first pregnancy) at the age of 30, neutropenia was more severe and complicated by repeated urinary tract infections. G-CSF was continued during pregnancy. She gave birth by vaginal delivery at 40 weeks' gestation to a male. At day 3 of birth, blood analysis showed 0.23 G/L neutrophils. He was treated by antibiotics (cefotaxime, amikacin, and vancomycin) and G-CSF because of *Proteus* and *Staphylococcus aureus* in the gastric fluid. The neutrophil count was 2.6 G/L at day 26. G-CSF was discontinued at 4 months with spontaneous and lasting normalization of the neutrophil count. *ELANE* gene sequencing did not identify any pathogenic variants.

Case 3

A 35-year-old woman was known to have autoimmune neutropenia since the age of 28 (lowest absolute neutrophil count: 0.5 G/L) with strong positive (+++) anti-neutrophil IgG by GIFT (IgM negative); GAT was negative. She had Hashimoto thyroiditis. For her third pregnancy (previous pregnancies: one abortion and one uncomplicated pregnancy) to a girl (weighing 0.825 g) by Caesarian delivery at 28 weeks +4 days' gestation (because of abnormal fetal cardiac rhythm and stunting in utero). At birth, the neutrophil count was 0.15 G/L. The child was admitted to intensive care for mechanical ventilation for hyaline membrane disease. A maternal–fetal infection was suspected owing to respiratory degradation and biological inflammatory syndrome. Vaginal swab showed *Escherichia coli* at 10^3. Antibiotic therapy with cefotaxime, amoxicillin, and gentamycin was administered until day 3 (sterile final infectious specimens: trachea, gastric fluid, pharynx, blood cultures). At day 29, the child presented with a respiratory distress with reintubation. Tracheal and pharynx cultures showed 10^4 of coagulase-negative *Staphylococcus*, which was treated with cefotaxime, vancomycin, and gentamycin. During the first week of life, neutrophils ranged from 0.15 to 0.3 G/L and at day 8 the rate was 1.56 G/L. Between days 32 and 34 she received G-CSF. Neutrophil count fluctuated between 0.65 and 2.9 G/L until 3 months of age, and then normalized. Anti-neutrophil antibodies were negative in the child and *ELANE* gene sequencing did not identify any pathogenic variants.

Case 4

A 30-year-old woman was known since age of 24 to have idiopathic neutropenia (range of the absolute neutrophil count between 0.36 and 1.16 G/L). Anti-nuclear and anti-neutrophil antibodies (flow cytometry) were negative. She did not receive G-CSF and did not have any infectious complications. She gave birth at 41 weeks' gestation by vaginal delivery to a girl. At birth, the neutrophil count was 0.37 G/L and this normalized spontaneously at 4 months. There were no infectious complications.

Discussion

Figure 1 reports the temporal evolution of the neutrophil counts of the four patients.

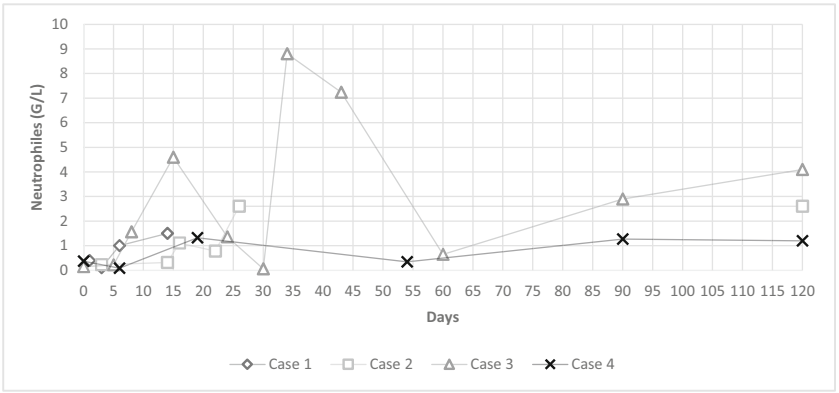

Fig. 1 Temporal evolution of the neutrophil count of the four children

Neonatal neutropenia secondary to isolated maternal autoimmune neutropenia remains largely unknown and only 14 cases (11 mothers, 14 newborns), including these, have been reported to date (Table 1).

Stefanini et al. [9] first reported in 1958 two patients with "a new syndrome: transitory congenital neutropenia." The first case was a 33-year-old woman with chronic neutropenia (lowest <0.5 G/L). A leukocyte agglutination test was positive with the inactivated patient's serum and the gamma globulin fraction. In vivo, severe neutropenia developed in the recipient for 2.5 days. The serum of the recipient agglutinated normal white cells for 4 days, including her own collected before the administration of the leukopenic serum. The patient's first pregnancy was uneventful with continuous antibiotic therapy. She delivered a girl at term. The infant's blood was identical to that of the mother (at birth leukocyte agglutination with a titer of 1:32). The severe neutropenia persisted for 3 weeks. The second case was a 39-year-old woman who had neutropenia during her fourth pregnancy (two children aged 6 and 4, one abortion). Neutrophil count had been normal several months before. Test to demonstrate anti-leukocyte factors were negative. The child had severe neutropenia at birth. Normal values were reached at 4 weeks. The child's serum did not exhibit agglutinins against white cells. The mother had a fifth child a year later. The child was born with neutropenia, which disappeared within 4 weeks.

Neutropenia was due to the trans-placental transmission of a non-identified neutropenic factor, which could be transferred to a normal recipient and was capable of agglutinating normal leukocytes. An antibody was suspected.

Van Leeuwen et al. [8] described in 1983 a transient neutropenia and a gradual disappearance of neutrophil-antibodies

Table 1 Literature review

Case (reference)	Mothers				Children				
	Lowest ANC G/L	AAN	G-CSF before gestation	G-CSF during gestation	AAN	Lowest ANC G/L	Infection	G-CSF	Neutropenia duration (weeks)
1	< 0.5	–	Yes	No	–	0.1	No	No	2
2	0.2	–	Yes	Yes	–	0.23	Yes	Yes	16
3	0.5	+	No	No	–	0.06	Yes	Yes	12
4	0.36	–	No	No	–	0.09	No	No	16
5 [5]	–	+	Yes	No	–	–	Yes	Yes	–
6[a] [5]	–	+	Yes	Yes	–	0.43	No	No	–
7 [8]	–	+	No	No	+	0.1	Yes	No	16
8 [6]	0.36	+	No	No	–	0.1	Yes	Yes	4
9[a] [6]	0.36	+	No	Yes	–	0.8	No	Yes	8
10 [9]	<0.5	+	No	No	+	<1	No	No	3
11 [9]	<0.5	–	No	No	–	<1	No	No	4
12[a] [9]	<0.5	–	No	No	–	–	No	No	4
13 [7]	<0.3	+	No	No	+	0.25	Yes	No	9
14 [7]	–	+	No	No	+	0.18	No	No	17

AAN autoantibodies against neutrophils, *ANC* absolute neutrophil count, *G-CSF* granulocyte colony-stimulating factor

[a] Same mother

in a newborn whose mother had autoimmune neutropenia. A 20-year-old woman with skin infections and buccal ulcerations was diagnosed with neutropenia. GIFT showed IgG antibodies against neutrophils. She became pregnant at the age of 24. Umbilical cord blood showed a very low neutrophil count and IgG antibodies against neutrophils were detectable with GAT and GIFT. On the third day of life the child developed pustulosis and an umbilical infection due to *Staphylococcus aureus*. After 16 weeks, the neutrophil count was normal and GAT was negative. This supports the theory that antibodies were passively acquired by transplacental transmission.

Neutrophil-binding IgG presence examined by GIFT in two supplementary cases in newborns were reported by Kameoka et al. [7]. The mother in the first case was a 31-year-old primigravida. She was diagnosed with neutropenia (<0.3 G/L) during gestation. The infant developed severe neutropenia immediately after birth (0.5 G/L). On day 8, he suffered from impetigo which was relieved by intravenous cefazolin and gamma globulins. The infant's neutropenia improved gradually (normal neutrophil count at 65 days). In the second case, the mother was a 37-year-old woman admitted at 27 weeks' gestation because of leucopenia and thrombocytopenia. GIFT was positive. She had been diagnosed as having idiopathic thrombocytopenic purpura (ITP) 14 years earlier. Her first pregnancy ended in a stillbirth at 28 weeks' gestation. The second and third pregnancies resulted in normal full-term deliveries with no complications. Severe neutropenia was observed at birth in the fourth child, without any signs of infection. The neutrophil count increased gradually and was normal at day 125.

The mother's neutrophil-binding IgG intensity remained positive after delivery in both cases. The intensity in newborns decreased and became negative in both cases (at days 121 and 84 respectively).

Davoren et al. [6] reported the occurrence in two siblings of severe neonatal neutropenia. Maternal serum contained an antibody that reacted with neutrophils by flow cytometry. MAIGA was negative. The first infant, a girl, was born at 26 weeks' gestation by Cesarean section because of a breech presentation to a 33-year-old (para 1 gravida 1) woman following an uneventful pregnancy. The mother's neutrophil count was 1.9 G/L at childbirth. No blood count was done before discharge at day 6. At day 11, she developed sepsis and was admitted to intensive care with severe neutropenia (< 0.1 G/L). She was diagnosed with *Citrobacter* meningitis and treated with intravenous antibiotics (ampicillin and cefotaxime), a single dose of immunoglobulin and G-CSF (between days 13 and day 16 and for 7 days 2 weeks later). The child had severe neurological sequelae and survived to 4 years of age.

During the next 6 years the mother continued to have neutropenia but she had no infections. For the second pregnancy, she received low-dose G-CSF from 32 weeks' gestation. She delivered a healthy girl at 37 weeks' gestation. The child's neutrophil count was 4.5 G/L at birth. White blood cells were monitored. During the next 3 weeks the absolute neutrophil count was measured progressively, reaching 0.8 G/L at day 20. Five injections of G-CSF were administrated between days 2 and 61 and two additional doses on days 61 and 64. The child was doing well at 9 months with a neutrophil level within the low normal range.

Fung et al. [5] reported the case of a neutropenic woman who had two pregnancies. She had been on prophylactic G-CSF treatment but stopped it before conception. The first pregnancy was complicated by premature rupture of membranes at 34 weeks' gestation. The female child had respiratory distress and severe neutropenia requiring admission to intensive care unit for ventilatory support. G-CSF was given. Neutrophils serology investigations were not performed. The baby recovered well.

In the second pregnancy, G-CSF treatment was introduced in the third trimester. The second infant had no neutropenia at delivery but the count declined in serial follow-up samples (lowest neutrophils: 0.43 G/L at week 7). He had no infectious complications.

After eliminating infectious etiologies and complications related to pregnancy, diagnoses to be evoked in the presence of neonatal neutropenia are congenital, allo-immune and autoimmune neutropenia.

Congenital neutropenia is a rare condition, observed in less than 1/100,000 people [10]. It encompasses a family of neutropenic disorders, both permanent and intermittent. It can also affect other organ systems (skin, muscle, bone, heart, central nervous system, etc.). The major risk remains leukemic transformation. It is usually related to gene mutations, such as *ELANE*, *GATA2*, *HAX1* (Kostmann disease) or *SBDS* (Shwachman–Bodian–Diamond Syndrome) [11]. Because of clinical heterogeneity, the next-generation sequencing (NGS) approach appears to be the most efficient strategy. Gene analysis by NGS or other approaches is only indicated after the most common causes are ruled out, in the case of persistent neutropenia associated with suggestive hematological or extra-hematological symptoms.

Primary autoimmune neutropenia is not suspected in neonates because it is exceptional at less than 1 month of age. The median age at diagnosis is 7–9 months and patient's remittance occurs after 2 or 3 years [1, 2, 12].

Two uncommon causes, probably underdiagnosed, are allo-immune and immune neutropenia secondary to autoimmune maternal neutropenia. Both are secondary to placental transfer of maternal allo- or auto-antibodies directed against neutrophil antigens. In contrast to genetic defects they resolve spontaneously.

Neonatal alloimmune neutropenia is due to feto-maternal granulocyte mismatch. The pregnant woman demonstrates

immunization against the paternal granulocyte antigens. The mothers do not have neutropenia. There is positive cross-match between maternal sera and paternal granulocytes. The incidence of neonatal alloimmune neutropenia is classically reported to be 1 in 6,000 newborns [2]. The mother produces IgG antibodies against fetal neutrophil antigens (anti-HNA1, also called NA1 or NA2, which are motifs of CD16 or Fc gamma receptor III), carried by the father's neutrophils and absent in the mother. There is a risk of recurrence for subsequent children. Infections are present in 1 out of 5 patients. The duration of neutropenia is on average 1–4 months [13].

Neonatal neutropenia secondary to maternal autoimmune neutropenia is the rarest form of immune neutropenia of early infancy, with 14 patients included.

Granulocyte autoantibodies were highlighted in 1978 [14] by the immunofluorescence test.

The combination of GAT and GIFT using a panel of typed and freshly isolated granulocytes is currently the recommended laboratory procedure for human neutrophil antigen (HNA) antibody detection. Panel reactivity can indicate antibody specificity, which can be confirmed by MAIGA. MAIGA is a glycoprotein-specific assay using monoclonal capture antibodies and has special importance in identifying mixtures of both HLA- and HNA-specific antibodies. Negative results in MAIGA do not necessarily indicate false-positive reactions in the screening tests and may be due to the non-existence of suitable capture antibodies, steric hindrance or the prozone phenomenon. Furthermore, IgM antibodies are not detected by GIFT, but can induce aggregation in GAT [15]. Interpretation of the test is difficult and must be done in collaboration with biologists. False-negative tests are common.

Antibody detection tests are not necessarily useful in newborns. A direct test is of uncertain significance and is not generally possible owing to extreme neutropenia. The genotype of the child is possible for the HNA-1 system. For other systems, the phenotype can be achieved only during the recovery of the normal neutrophil count. In this situation, genotyping of parents can be helpful and allow withdrawal of the child's blood to be restricted.

In half of the cases previously described, autoantibodies against neutrophils (AAN) were positive in mothers (7 out of 11). In some newborns tested (3 children), IgG^+ AAN were also positive, with disappearance in parallel of spontaneous neutrophil count improvement [7, 8]. No correlation between maternal type of autoantibodies and titer and neonatal neutropenia has be established so far. None of our cases presented a mismatch between maternal and paternal neutrophil antigens.

In cases tested negative for AAN, an autoimmune mechanism is strongly suspected, because in all these cases neutropenia resolved spontaneously.

Whatever the cause of neutropenia, bacterial infections are the main clinical manifestations.

Six out of 14 children had infections. Morbidity was important: all children required hospitalization (between 2 weeks and 1.5 months). All required intravenous antibiotics. Three were treated in intensive care unit. The germs involved were: *Citrobacter* meningitis, *Proteus* and *Staphylococcus aureus* in gastric fluid, *Staphylococcus aureus* pustulosis and umbilical infection, pneumonitis due to coagulase-negative *Staphylococcus*. One child had impetigo.

Infections in neutropenic patients were primarily cutaneous. As in our patients, typical pathogens are *Staphylococcus aureus* and coagulase-negative, Gram-negative *Enterobacteria*, *Enterococcus* and *Streptococcus* species, and *Pseudomonas aeruginosa* [16].

Three children were premature: 36 weeks (cesarean section because of breech presentation), 34 weeks (premature rupture of membranes), and 28 weeks +4 days (cesarean section because of abnormal fetal cardiac rhythm and stunting in utero).

Organisms most frequently involved in early-onset neonatal sepsis of term and preterm infants together are group B *Streptococcus* and *Escherichia coli* (70%). Additional pathogens to consider are other streptococci, *Staphylococcus aureus*, *Enterococcus* species, Gram-negative enteric bacilli, *Haemophilus influenzae*, and *Listeria monocytogenes*.

When preterm and very-low-birth-weight infants are considered separately, the disease's burden attributable to *E. coli* and other Gram-negative rods is increased, making Gram-negative sepsis the most common etiology. Many episodes are managed empirically (no pathogen isolated) [17].

Infections did not correlate with neutrophil count nadir in mother or in child.

Three mothers had G-CSF during pregnancy. One newborn reported in literature with a severe infection (*Citrobacter* meningitis) had severe neurological sequelae, with early death [6]. G-CSF was administered to the mother during her second pregnancy. The newborn did not have neonatal infection. Absolute neutrophil count was normal at birth but decreased progressively over the following weeks.

A similar case was reported by Fung et al. [5]. G-CSF administered in the last trimester had no adverse effects on the second infant. He presented no infection. However, no improvement in the neonate's blood cell count was observed immediately after delivery. A possible explanation is that the half-life of G-CSF is shorter than that of the antibodies.

The third mother (case 2) presented during pregnancy a worsening of neutropenia and repeated infections. G-CSF was continued. The infant had neutropenia at day 3 and presented infectious complications.

G-CSF was administered to 5 newborns in the case of severe infections (except for cutaneous infections) with no adverse effects. In a 2003 Cochrane meta-analysis [18] no toxicity of G-CSF used in infants was reported.

Three observational studies recently reported outcomes associated with the administration of G-CSF to pregnant women [19].

In one study (107 women, 224 pregnancies), treatment with G-CSF (median dose 1.0 mcg/kg per day) in spontaneous terminations or preterm labors was suggested to be a benefit [20]. Adverse events in the neonates were similar for the two groups (included preterm labors). Another study analyzing 38 pregnancies (21 women) showed no difference in outcomes with or without treatment for the mothers or their newborns [21].

G-CSF in children may be helpful in severe neutropenia and a major risk for infection [22]. A retrospective study of 30,705 neutropenic infants in intensive care and 2,142 treated with G-CSF (7%) showed that G-CSF shortened the time for hematological recovery, but did not reduce secondary sepsis or death at 14 days compared with untreated infants [23].

In the case of severe neutropenia, any sign of infection leads to an emergency infectious assessment and to starting intravenous probabilistic antibiotherapy active on Gram-negative bacilli and Gram-positive cocci. In the case of serious infection, it is recommended to approach a pediatric hematology department to discuss G-CSF treatment.

Conclusion

In conclusion, we report here four new cases of neonatal neutropenia secondary to maternal autoimmune neutropenia and a brief literature review of the cases reported. From the few cases reported so far it is impossible to draw any conclusions regarding frequency, risk factors, and outcome, but the overall prognosis for the newborn seems good. Because it can be associated with potentially severe neonatal infections autoimmune neutropenia in childbearing mothers should be closely monitored in collaboration with gynecologists and pediatricians.

It has been reported that low-dose G-CSF administered to childbearing women during pregnancy could be proposed in some cases to prevent newborn neutropenia. However, the frequency of neonatal neutropenia in women with autoimmune neutropenia and the risk of recurrence in subsequent pregnancies are both unknown. It is therefore not easy to predict neonatal neutropenia and guide the indication for G-CSF therapy before birth.

The severity of the infections presented by children encourages us to systematically check the rate of white blood cells at birth, with prolonged close monitoring as in idiopathic thrombocytopenic purpura. G-CSF must be started early in the case of infectious syndrome to recover a sufficient level of neutrophils. An absolute neutrophil count higher than 1 G/L could be suggested.

Compliance with Ethical Standards

Conflicts of Interest The authors declared that they have no conflicts of interest.

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