Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/alloimmune-neutropenia-of-the-fetus-and-newborn/13910/

Released: 12/29/2022
Valid until: 12/29/2023
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Alloimmune Neutropenia of the Fetus and Newborn

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Alloimmune Neutropenia of the Fetus and Newborn” is provided by Omnia Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Shulman:
Neonatal alloimmune neutropenia, known as NAIN or NIN, is a neutrophil blood group antagonism. It's analogous to hemolytic disease of the fetus and newborn, or HDFN, and fetal neonatal alloimmune thrombocytopenia, or FNAIT. While the incidence of NAIN is not precisely known, symptoms vary from none to severe infections including pneumonia, sepsis, and meningitis, making it critical that we diagnose and treat it appropriately.

This is CME on ReachMD, and I'm Dr. Lee Shulman. And I'm happy to say that we're joined today by an international expert on this particular condition, Dr. Masja de Haas, from the Netherlands. Dr. de Haas, welcome.

Dr. de Haas:
Hi, I’m Masja de Haas. I'm working as an immunohematology consultant in the Netherlands in the National Reference Laboratory of Sanguin Diagnostic Services in Amsterdam. I'm excited to contribute to this podcast on NAIN.

Dr. Shulman:
Dr. de Haas, welcome. And let's dive right in.

This disorder is rare and complicated, but I understand that you have a brief case study that will demonstrate the importance of proper diagnosis and treatment.

Dr. de Haas:
Yes, indeed. Also, in one of the recent cases in which we performed a laboratory workup for NAIN, it was striking how much concern there was at the site of the referring physician. And here it concerns an 8-day-old baby that was suffering from an omphalitis, and there was not yet a full separation of the cord. So a special situation. And the blood counts showed an absolute neutrophil count of 200 per microliter, whereas all the other lineages showed normal counts. And the pediatrician who called us was worrying that this was the first sign of a neutrophil defect in the child, and he had consulted the University Hospital for a referral. And his colleagues there, they advised him to call us to see if it here could concern NAIN. And that was a good thought. And, of course, NAIN, it can be very serious; it can have severe infectious problems. But in its nature, you can say it is benign, because in the end it will resolve. And indeed, for this case, we could confirm that it here concerned NAIN. And that was a great relief for the treating pediatrician and also for the mother and father of the child.

As you already said, it is rare, and that is completely true. It has been noticed, the condition, since 1960s, when it was first described by Professor Lalezari, who reported on the occurrence of the disease in 3 of 4 siblings, but it may occur in less than 1 in 10,000 babies.

And it may be clinically apparent only in a fraction of those. So indeed, it is a very rare condition.

Dr. Shulman:
Well, Dr. de Haas, asking you this next question, I probably couldn't ask a better person to tell us about the causes of NAIN, having been well published on this topic.

Dr. de Haas:
Well, I already mentioned Professor Lalezari who was the first to show the condition and also he was the first to show that it is caused by IgG-type antibodies that are developed by the mother and that react with paternal antigens on the neutrophils of the child. One can compare the disease with hemolytic disease of the fetus and newborn, or HDFN, which, for example, can be caused by anti-D that a mother can develop if she is RhD negative and her child is RhD positive. And it it's a similar condition. For the neutrophils, we now consider 5 different human neutrophil antigen systems, so-called HNA systems, and that are the blood group antigens of neutrophils. And they can all be involved in the condition.

So it may be that during pregnancy, some neutrophils of the child enter the maternal circulation and that the immune system of the mother is triggered to develop an immune response against the foreign HNA blood groups of the child. And if the mother develops antibodies of IgG class, these will be actively transported over the placenta to the child and bind to the neutrophils of the baby. And this will lead to destruction of those neutrophils. And it may also impair the formation of neutrophils in the bone marrow.

So, in most cases, it conserves HNA type 1 antibodies, and HNA-1 is expressed by one of the IgG Fc receptors of neutrophils. This is also called a CD16. And even so-called isoantibodies can be developed if a mother is CD16 deficient.

And the second most important human neutrophil antigen blood group system that you may remember after this podcast will be HNA-2, because also HNA-2 can be involved in NAIN.

Dr. Shulman:
Dr. de Haas, in the case you presented, the baby presented with an infection of unknown etiology, and the baby underwent a CBC and included a white blood count, and that was the hint. But if we do suspect that our patient has NAIN, what exactly are we looking for? And what are the clinical manifestations? And how do we go about ultimately making the diagnosis?

Dr. de Haas:
Indeed, the clinical manifestation is, first of all, a reduced absolute neutrophil count. And that is in most cases already present at birth. But neutrophil counts may decrease in first weeks postpartum. And that low number of neutrophils can last for approximately 6 months. And the second sign of the disease is that a bacterial infection may occur. But in many cases, NAIN also will resolve completely unnoticed. So it can have a very mild clinical course.

And another important sign of the condition is that there is a delayed separation of the cord, because neutrophils are needed to separate the cord. And what we also know is that in most severe cases of NAIN, so in children that have clinical symptoms, their neutrophil counts are below 500/µL. So it is the neutrophil counts and the infections that occur.

And to diagnose NAIN, it requires a specialized reference laboratory to perform the testing that you need. And there are several of those laboratories worldwide. And fortunately, they also work closely together in one of the working parties of the International Society of Blood Transfusion to advance the knowledge of NAIN and to compare laboratory technologies, because there are not that many techniques available to reliably detect those HNA-specific antibodies.

Dr. Shulman:
Let me just add one thing for our listeners. I think, as you've heard, this would be something that a neonatologist or a pediatrician should be considering for that child whose cord is not separated yet and who may have low neutrophil counts. But I think as you've just heard from Dr. de Haas, it's important to recognize that ultimately, the diagnosis has to be made in a specialty laboratory. So for our clinicians here, there should be a consideration of this when we have that unique presentation. Ultimately, though, it's going to be a hematological specialist and the laboratory that they use that's ultimately going to make the diagnosis.

In that regard, Dr. de Haas, what are the treatment options that are available?

Dr. de Haas:
Yeah, well, there are, of course, if there is an infection, one will start with the appropriate type of antibiotics. And in the small case series that have been published on these cases, it has been shown that in most of the cases it is sufficient. And some recovery is fast, within a week to 1 month. And then in others, it lasts for 3 to even 4 months before the neutrophil counts normalized. And so you have to decide if you need to continue the antibiotic treatment in that period. And that is a case-by-case decision that the clinicians should make. And if there is a severe disease and absolutely no recovery of neutrophil counts, then second-line treatments can be considered. And that can

be intravenous immunoglobulins or IVIG. That is started sometimes, but there is no evidence that it will be effective in NAIN. But I know that clinicians are considering it as a treatment policy.

And definitely another treatment option that can be considered is granulocyte colony-stimulating factor, or G-CSF, and that can be considered in life-threatening cases of infections and if there is absolutely no sign of recovery of the neutrophil counts. Then G-CSF may be used to accelerate bone marrow recovery.

And what I see in the Netherlands is that because the disease is so rare, that it is important to discuss it in multidisciplinary settings to decide on the treatment, especially because it can differ case by case.

Dr. Shulman:
I couldn't agree with you more. I think the critical issue here is a primary care neonatologist or pediatrician that is sort of cognizant of the potential for NAIN, and then being able to provide the referral to the appropriate hematological specialist who has access to a specialty laboratory.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Masja de Haas. We're just about to transition our discussion to what the community obstetrician needs to know about NAIN.

So, Dr. de Haas, let's get back to basics and break this down into actionable clinical tips. What does that community obstetrician need to know about NAIN?

Dr. de Haas:
Yeah, that's a great question. And it's a question that obstetricians have, and of course, also a question that parents have. What is the risk of occurrence in a next pregnancy? And the risk depends on the type of antibodies that are developed. So it concerns certain inheritable antigen systems. So if the father is homozygous for such a system, then the risk of occurrence in the next pregnancy is 100%. But otherwise, it can also be 50%. It really depends on what antibody and what system is involved.

And since no problems are expected in the antenatal period, we are not performing fetal blood group antigen typing with cell-free fetal DNA for this condition. We are also not performing a follow-up of antibody titers in pregnancy. But of course, immediately after birth, the child should be checked for signs of infections and blood count needs to be performed. And yeah, you can check what the HNA type is and some limited laboratory testing that can be very informative and also reassuring if a child is negative for the antigen concerned.

The only thing I wanted to say is that what we are seeing in subsequent pregnancies of couples that have had a previous child with NAIN, that in most cases prophylactically, antibiotic therapy is started in such a next child when the disease could occur because of positivity for the blood group antigen involved.

Dr. Shulman:
Well, I think you bring up an important point, especially in those couples for which the father, whether he is a heterozygote or homozygote, the possibility of prenatal diagnosis exists, and the possibility of preimplantation genetic testing exists, as well as the possibility, although perhaps not the most optimal choice, but the possibility of gamete donation to have in particular for those that fathers that are homozygous for the particular antibody to allow for a pregnancy that will be unaffected with this condition. And so as a result, counseling becomes an important aspect of this after the appropriate testing for parents who've had an affected child has been undertaken.

Dr. de Haas, what are your main take-home messages for our audience?

Dr. de Haas:
Well, I think that we made clear that NAIN is a rare condition, but that the consequences can be serious and that it is important to have it as a differential diagnosis to ensure that the appropriate testing is done and a treatment is started, and also to have the reassurance that there is no neutrophil defect present. I think that therapeutic and prophylactic treatment with antibiotics will be most often effective and be sufficient. And that you should be aware of the condition in a next pregnancy and test the newborn directly after birth and start, if necessary, prophylactic antibiotic treatment at that moment.

Dr. Shulman:
We obstetricians and obstetrical providers need to potentially dig a little deeper when they find out that a previous pregnancy was affected with some sort of bacterial infection. And in particular, look to see whether in that workup, was there a concern regarding the immunological impact on the baby's ability to mount an adequate response? And if the answer to that was no, then to find out exactly what that immunological issue was. Obviously, referral to maternal fetal medicine in certain cases, but to get the kind of information so that we as obstetrical providers can provide appropriate care in future pregnancies.

Dr. de Haas, unfortunately, that's all the time we have today. So I want to thank our audience for listening in, and I want to thank you for joining me and sharing all of your valuable insights. It was great speaking with you today.

Dr. de Haas:
Well, thank you very much.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Omnia Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Omnia. Thank you for listening.