

MS. GIRAND:

Dr. Rock, thank you very much, very much. And we will now have the question and answer period we've been talking about. And what we will ask is participants please come to the microphone and please ask your questions at the microphone. Again, give your name, if you would, please, and we will direct questions to Dr. Lingwood and Dr. Rock, and we will double check that Nancy has a microphone for Dr. Rock.

DR. ROCK:

Let me just put this stuff down, here.

MS. GIRAND:

No questions?

DR. ROCK:

My question is where is Dr. Lingwood?

MS. GIRAND:

Go ahead.

MS. SEE:

Dr. Rock, thank you very much.

MS. GIRAND:

Could you please give your name?

MS. SEE:

My name is Ann See, and my daughter is 16 years of age and was infected, and she's doing well now. She's quite something. But you mentioned several times in your speech about things that patients can be aware of to plan ahead and be aware of looking for so that they can be in connection with their physicians.

And, as you mentioned, one of your patients came to you and said, you know, I've noticed this, is there something we need to look for and to do.

Do you have any lists that you can share with the general public so that they know what to look for?

DR. ROCK:

I think actually, as far as I know in the United States, there's also a TTP support group, but I think that the recommendations from that group would be pretty much the same as in HUS. And while I recognize that many people in the room today are primarily involved with the pediatric form of -- of HUS, which is E. coli initiated in most cases, I would suggest to you that final common manifestations of both of these disorders are the same. You end up getting platelet microthrombi to plug up your kidneys.

And when that happens, of course, your platelet count drops. We have found by and large the very best indicator of early disease is that platelet count. So people can just watch out for the easy bruising, clotting of any nature; that's the best we've seen.

But by and large the pediatric HUS does not tend to reoccur, although I find this interesting in itself, because as Dr. Lingwood said, you don't really build antibodies against it. In fact in the majority of patients in one of our other studies we are doing (where we are trying to separate the STX positive versus STX negative patients in order to see if they do respond differently) even when we are pretty sure we've got a patient with bloody diarrhea, etcetera, Health Canada's doing the assays for us and we are getting negative results for STX antibodies.

Maybe you would like to comment?

DR. LINGWOOD:

Well, I'm not involved in the etiology group, epidemiology studies, but that is consistent with what I said that the toxin has targeted B cells and prevents antibody production.

One thing I did mention in my talk was on one slide, as somebody noticed, is that B cells are also the prime targets of antigen presentation. So foreign antigen has to be processed inside cells and broken down and expressed in the context of possible T cell recognition.

And so these cells, the antigen presenting cells, are also potential targets.

MS. SEE:

Thank you.

SPEAKER:

Dr. Rock, you mentioned that most of us are here because of food or through --

DR. ROCK:
E. coli food-related.

SPEAKER:
Right.

DR. ROCK:
That was my perception. I could be quite wrong.

SPEAKER:
Could you tell me: Is TTP a result of a food-related bacteria?

DR. ROCK:
Dr. Karmali (phonetic) from the Sick Children's Hospital in Toronto did some assays on some of our patients several years ago. And we took 35 adult patients and found, in fact, the antibody to be present in about 20 of those 35 patients.
But he was very uncomfortable with the results because we didn't have an adult to do follow-up studies and see whether the antibody was broken down. So we never did publish that data.
But in our new series that was taken off of this study those assays will be done by Hal Cameron (phonetic).

SPEAKER:
Can you tell me then what are the causes of TTP?

DR. ROCK:
When I was coming in last night on the flight, I was reading the Journal of Transfusion and they documented a case of Staph aureus induced TTP. The list was getting pretty long.
Now, previous studies have always gone back and looked for an acute infectious agent and there has rarely been a good association, unlike the bloody diarrhea, E. coli, HUS. But it would seem as if a number of initiating events are possible. They could be different bugs that could be drug induced. We know post transplant a lot of people that developed TTP again.
Whatever the insult is we appear to be ending up with a final common pathway of activated platelets which stick together and stick on the endothelium for some reason.

DR. LINGWOOD:
I think maybe what one of the distinct features of HUS and TTP will turn out to be is that one requires Gb3 reactive toxin and the other does not. The other is microangiopathy due to some other cause. But the upstream to that is maybe quite distinct.

DR. ROCK:
I would remind any of you who are in the medical profession that there are other diseases and disorders in which, in fact, platelet activation is antibody mediated.
So I think we are just in an exciting time of working our way through these reactions now.

MS. GIRAND:
Please give your name.

MS. RIGERT:
I'm Jennifer Rigert. I contracted HUS 26 years ago as an infant and received a kidney transplant about three years ago. And I am currently being treated with cyclosporin.
Dr. Lingwood, I'm not sure I heard you right, did you say that cyclosporin induces HUS?

DR. LINGWOOD:
Yes, that is the case, it can be. A prolonged use of cyclosporin is one of the drugs which has been reported to be associated with HUS, yes. But the cyclosporin you've been given for the moment is to prevent the graft rejection. So it's a balance, here.

MS. RIGERT:
So am I now more susceptible to HUS again?

DR. LINGWOOD:
I think that the HUS associated with cyclosporin is in high doses, so I would say not from that, no.

MS. RIGERT:

Thank you.

DR. ROCK:

Just a comment that a number of other drugs have been implicated in HUS as well and have been implicated in inducing HUS.

MS. JACKSON:

Cam Jackson, this is for Dr. Lingwood. You mentioned about HUS or E. coli being identified in cattle, exactly when did that happen?

DR. LINGWOOD:

Sorry, exactly when?

MS. JACKSON:

Yeah, when was it identified as cattle being the carrier?

DR. LINGWOOD:

The carrier?

MS. JACKSON:

Yes, has it been quite some time?

DR. LINGWOOD:

Oh, a long time, yeah.

MS. JACKSON:

When my son had HUS he was, well, it was 11 years ago, and we were told such little about it that we have no idea how he contracted it. It was not food. He was a baby.

DR. LINGWOOD:

At the time verotoxin was identified as being the cause of HUS in 1985. It was then known that verotoxin E. coli were in cattle.

MS. JACKSON:

My husband is an ag teacher, that's why that tends to be something we're interested in. Thank you.

MS. BOULAHANIS:

Hi, my name is Kara Boulahanis, and I was wondering: Is there any connection between autoimmune disorders and HUS?

DR. LINGWOOD:

Not that have been reported, that we're aware of, no.

MS. BOULAHANIS:

Because my family, all three of us, all contracted HUS and all three of us right now have autoimmune disorders. And it's only been seven years or eight years now since we've had it and it seems like a really insane coincidence.

DR. LINGWOOD:

Well, certainly antibodies to carbohydrates are associated with autoimmune diseases, and I could see the possibility that if you had a verotoxin induced HUS, you might develop an altered exposure of the glycolipid. It's feasible that that could occur but as far as I'm aware of, no one has ever suggested that that is a sequela of the infection.

DR. ROCK:

Maybe I could comment. I would remind you of the data on TTP, now, in which it looks like people develop antibodies against a protease they have in their own body normally. This is the acute presenting form. This is by no means found in all patients, but that would classify as an autoimmune disease of TTP.

As I have suggested to you, Dr. Furlan has looked at patients with TTP, and so have we, and not found that same antibody present in HUS patients. But it is indeed possible that HUS could ultimately be an immune mediated disease. And perhaps you and I could have a little chat further some time today.

MS. BOULAHANIS:

Thank you.

MR. SANTUNI:

My name is Paul Santuni, from Scotland. I have a question for Dr. Rock, back to plasma exchange. Did plasma infusion in the case of treating the elderly that you discovered in Canada were severe cases of TTP or HUS whether either infusion or exchange result in the short term benefits i.e. sub seven days as opposed to the six month information that you have?

DR. ROCK:

We exchanged some of the patients from a most recent outbreak of the E. coli disease that we had. And they appeared to respond in the same way.

Unfortunately, some of them were not referred early enough into us to be able to get a good comparison.

I've not seen any particular effect on the elderly. Although I am aware that you had an outbreak several years ago of a disease primarily in an elderly population. Could you comment?

MR. SANTUNI:

Yes, there have been at least 21 elderly people that have died. I was called to represent a substantial number of the people in relation to these cases. And subsequently, in the Scottish outbreak where we had the elderly dying, quite a few of the conditions were not properly identified, first of all. We had either cases of plasma exchange, usually plasma infusion, that we got to quite a few of the people, but more often than not physicians were not making it available, and treating at home, which is really ineffective. The result was we had several people willing to develop TTP and again with the incompetent infusion and exchange.

And from what I remember, it was suggested that the different exchanges and infusions had an impact on morbidity and survival between these exchanges and infusions in regards to the morbidity and survival, though infection was acquired but nothing that we've been talking about was brought up at any point with medical, scientific evidence.

DR. ROCK:

Well, Walkerton, itself, does not have a plasma exchange unit, and so these patients were referred via London or Hamilton. And I would certainly suggest to anyone who is confronted with a patient and doesn't have immediate ability to exchange that infusion would be a good way to start.

MR. SANTONI:

Thank you.

MS. DAY:

Hi, I'm Laura Day. I had HUS and TTP as an 18 year old, seven years ago. And I received 19 plasma apheresis treatments while I was in the hospital with fresh frozen plasma. It worked for a while. My blood count would go down again, then up, about as low as 8,000 at one point and eventually that wasn't working anymore and they removed my spleen. And I've been okay. Since then, I have a few immunity issues, myself, but my question is: Do you have an opinion on the removal of the spleen as treatment in this case and if there is a recurrence will not having a spleen hurt my chances?

DR. ROCK:

In the majority of cases at this point in time I think it's fair to say this splenectomy is not a number one, up-front therapy. It is not yet completely accepted in TTP that it is an autoimmune disease.

There is a good deal of evidence from my lab and Dr. Tsai's and Furlan's that one or another kind of antibody is involved in a thrombotic event in TTP.

On the other hand, before we had that evidence, splenectomy and corticosteroids let us say 10 years ago before the evidence on plasma exchange came up, splenectomy and steroids were used for therapy and the outcome was highly variable and probably not more than successful in 10 to 15 percent of the cases.

Now that we think that it's an autoimmune disease, there's no particular reason to believe that it's going to be any more effective.

On the other hand, when patients are refractory, as some 10 to 20 percent are through our standard therapies, now, then yes, I would certainly recommend going into splenectomy. I would use Staph. aureus columns to specifically bind antibody. A variety of immunosuppressants would also be considered.

MS. GIRAND:

One more question.

SPEAKER:

My question for you, Dr. Rock, with respect to children with HUS we've seen a lot of children who just receive plasma apheresis, we've seen children who just receive dialysis, and we've seen children with a combination of dialysis and apheresis.

I have not seen any literature on the efficacy of those treatments being compared, and I just wondered if you had any thoughts on that.

DR. ROCK:

I think you're right in terms of the fact that there's a fair amount of discrepancy in approach, and I think some of that depends on the relative frequency of the disease in any kind of a cluster in which someone would gather data.

Certainly we tried in Canada a few years ago to be actually addressing the pediatric population. And our clinicians were not particularly clean, but that is exactly at the same time that they were getting into the examinations of Synsorb and its capabilities of binding to the toxin, etcetera.

Plus the general thought that was expressed to us, admittedly on an individual basis, was that most of these kids get better, anyway.

Plasma exchange is not completely innocuous. There are side effects. Every couple of years in Canada out of our 10,000 procedures we will report one or two serious reactions and about every three or four years we have a death.

Usually that's related to a central line or other place places, however. But, nonetheless, these are all things that go into consideration.

MS. GIRAND:

Could you please give your name?

MS. MCINTOSH:

My name is Sarah McIntosh and my question -- I have two questions. The first one being is there a single determining factor between HUS with severe neurological complications versus TTP with severe renal complications?

DR. ROCK:

No. In my most recent rebuttal on a grant going back and forth on whether it would be funded it was insisted that I clearly and specifically define with our group of Canadian investigators the difference between the two.

And we spent a couple of weeks E-mailing each other back and forth just wrestling with this and finally came up with the fact that we would exclude from the study those that have bloody diarrhea two weeks prior, all right, and we can't even rely totally on the STS antibody assays because even though we've got gingival biopsy proving disease, we don't always get a correlation that you have a positive STS antibody.

I would argue to you at the present time that in any adult situation that we don't have enough information yet to make that distinction, though if Tsai and Furlan's assay holds up and metalloprotease is inhibited only in TTP and not in HUS, then maybe we will have.

MS. MCINTOSH:

My second question is: I've heard some speculation from the physician in New York that HUS might be somewhat related to a strep infection or can be caused by some kind of strep infection.

DR. ROCK:

A variety of insults have been considered over the years to be involved. Pneumococcus has been cited in some cases. There's a lot of different things. What you appear to need to do is kick that endothelium off and get some of these other reactions going.

MS. GIRAND:

This will be our last question.

MS. ROSENBAUM:

Hi, Donna Rosenbaum, I have a question for Dr. Lingwood. You talk about butyrates and the risk of developing the infection being greater, you thought, if butyrates were present in a -- in another infection simultaneous or preceding.

My question is: Do you think this would just affect the risk of developing the infection or would it also affect the incubation period.

DR. LINGWOOD:

No, this will affect the outcome of an infection so it won't increase the risk of infection but will -- would increase the severity of symptoms.

MS. ROSENBAUM:

You don't think that we have an effect on the incubation period of the --

DR. LINGWOOD:

The incubation period can be related to time between infection and symptoms. Possibly, yes, it could shorten

the time to symptoms; it would depend on the timing of the infection. So if the butyrate producing infection was there already, then your cells would be primed to respond to a subsequent infection of verotoxin producing E. coli. If it were a concurrent infection it would take some time to upgrade the receptor and then it probably wouldn't change the time to symptoms but would change the severity. So there's a lot of variables there.

MS. ROSENBAUM:

The reason I'm asking is I've encountered a number of people who have very short incubation periods.

DR. LINGWOOD:

It's a possibility they could have a butyrate producing infection earlier.

MS. ROSENBAUM:

They did have earlier disease processes going on.

DR. LINGWOOD:

It's definitely something we have to be looking at. You can present that to Dr. Tarr.

MS. GIRAND:

And that's a great segue. Thank you very much, Dr's. Lingwood and Rock, thank you.