Hi. This is Herb Kressel Editor of Radiology and welcome to the March 2017 podcast. This month we have a special extended panel discussion. We’re publishing three separate articles on gadolinium retention and have a panel discussion related to the three articles. So joining us will be Dr. Timm Denecke from the Virchow campus of Charite Medical Center in Berlin who with his colleagues wrote an article entitled “Is There Long Term T1-Weighted Signal Intensity Changes in the Central Nervous System After Gadoxetic Acid Exposure?” This is an agent that we have not learned about the gadolinium deposition after use. We’ll also be speaking with Dr. Alexander Radbruch of the Cancer Center in Heidelberg who with his colleagues wrote a provocative paper titled “No Signal Intensity Increase in the Dentate Nucleus on Unenhanced T1-Weighted MR Images After More than 20 Serial Injections of Macrocyclic Gadolinium-based Agents.” And the third author joining us is Dr. Paul Evans who if the director of non-clinical science, head of non-clinical science at GE Healthcare in Amersham. He and his colleagues did a longitudinal study entitled “Clearance of Gadolinium from the Brain with No Pathologic Effects after Repeated Administration of Omniscan in Healthy Rats: An Analytical and Histologic Study.” To round out our panel, we’re very, very fortunate to be able to have Dr. Manny Kanal, Professor of Radiology and Director of MRI Services at the University of Pittsburgh and Dr. Mike Tweedle Professor of Radiology at Ohio State University. Dr. Tweedle is a chemist who has been an active investigator and inventor of gadolinium based contrast; and Dr. Kanal has decades of experience and expertise in issues related to MR safety. This podcast is a bit longer than our normal ones, but I assure you it will be worth your while. Thank you. Next, my colleague Dr. Albert de Roos will interview Professor Bjorn Friebe of the Otto von Guericke University in Magdeburg, Germany. Dr. Friebe and colleagues wrote a manuscript entitled “Impact of in Vivo High-Field and Ultra-High-Field MRI on DNA Double-Strand-Break Formation in Human Lymphocytes.” This subject has been quite controversial and created a very significant stir in European Radiology and Cardiology and I think you’ll find this discussion quite informative. Thank you for your interest in the podcasts. We look forward to hearing from you.
Timm Denecke  Hello, thanks for inviting me.

H.Y.K.  Sure. And a return visitor, Dr. Alexander Radbruch who is a senior attending at the German Cancer Research Center in the Department of Radiology in Heidelberg, Germany. Welcome Dr. Radbruch.

Alexander Radbruch, MD  Hello. It’s a pleasure to be here. Thank you for inviting me.

H.Y.K.  Sure. And a newcomer to our podcast is Dr. Evans, head of Non-clinical Sciences at GE Healthcare Life Sciences in Amersham, UK. Welcome Dr. Evans.

Paul M. Evans, PhD  Hi. Thanks for the invitation. It’s great to be here.

H.Y.K.  Sure. Okay why don’t we begin? Dr. Kanal maybe you can set the stage for us. Where are we in our understanding of gadolinium deposition following gadolinium based contrast administration?

E.K.  Well it’s been almost three years since Dr. Kanda came out with his first revelation of the connection between gadolinium based contrast agents and intracranial, at least intracranial, parenchymal retention. We learned so much, but at the same time we’ve learned so little in the interim. We do know that there is retention that occurs with essentially all these agents, but it seems to occur more even significantly more with the linear agents than with the macrocyclic agents. We’ve learned that there’s a possibility of washout but there seems to be some conflicting data in that sense as well. We have learned that whether or not we see it on T1 shortening on images Dr. Murata and others have now found that there is significant (inaudible) retention for all agents regardless of their makeup whether they’re macrocyclic or linear; and perhaps most importantly is we still have no idea what the clinical relevance if any is of this finding.

H.Y.K.  Well thank you. That sort of it’s quite a story. We’ve learned a lot and yet we still seem to be at the beginning. Dr. Denecke you and your colleagues authored the first paper we’ll discuss, “Is There Long Term T1-Weighted Signal Intensity Changes in the Central Nervous System After Gadoxetic Acid Exposure?” And so it was kind of an interesting problem to look at the brains in patients receiving a liver agent. So what was the impetus for this study and how did you actually acquire head exams in patients receiving gadoxetic acid?

T.D.  Yeah well motivation for this study was of course to see whether in this it was virtually the last contrast agent of which we didn’t know whether there would be or not some accumulation in the brain and as we work a lot with liver imaging here and a lot with this special agent, we wanted to perform this study and as you said, it was quite difficult. We had to do extra scans and we couldn’t go in a retrospective fashion back to gadolinium naïve scans because those patients which we enrolled were all liver patients and only occasionally there has been some brain scan but the majority of the patients not.

H.Y.K.  I see. They were all liver patients, many or most of them were for surveillance for hepatocellular cancer and some had suspicions of metastatic disease. Is that correct?

T.D.  That’s correct but many patients as well especially when we go to those who had many follow-up scans every now and then with Primovist again and again. Those patients are from special surveillance programs, cirrhosis a few but also patients with neuroendocrine tumors which are (inaudible) with this specific contrast agent and as well from our minimally invasively treated patients with liver tumors.

H.Y.K.  Okay. Now you had a control group. You had 91 patients that received the gadoxetic acid and you had a control group. How was the control group acquired?

T.D.  We made a control group because we didn’t have the gadolinium naïve baseline scan and that’s why we thought it would be a good idea to have the control group to be compared. And the control group of course had to be gadolinium naïve as well. We casted those patients from neuroradiologic scheduled exams.

H.Y.K.  Okay so you for these patients you acquired an unenhanced T1-weighted scan before administering the contrast agents?

T.D.  Exactly.

H.Y.K.  Okay. And then tell us about the exclusion criteria. You excluded patients that had more than two prior MRIs with macrocyclics, but you also excluded patients that had any prior linear agent. Is that correct?

T.D.  That’s correct. I thought that would be important to not have any confounding factors in there.

H.Y.K.  Okay and where did the number of two come from for the macrocyclics?

T.D.  On the one hand, we did want to exclude any gadolinium based contrast agents, but on the other hand we wanted to have study cohort large enough and then we ended up with two estimating to approach a number of 100 patients.

H.Y.K.  So you divided them into three groups and the readers can see that you had one that had lower levels of exposure sort of mid and then the most number of previous exposures and what was sort of the average for the three groups?

T.D.  Yeah well this is kind of an arbitrary intervention in this study to have those three groups. I think the most important point is the correlation of the entire group of
gadolinium EOB exposed patients with a number of applications. But that’s the mathematically more important part, but on the other hand I wanted to get an idea of the clinical situation of the patient when he comes to me and also wanted to have three groups equally large. So I divided a cohort which is 91 patients by three and looked at the number of applications they had. We ended up with three almost equally sized groups with one to four, five to ten, and more than ten applications.

**H.Y.K.** I see. You looked like there was a relationship between the number of exposures and an increase in T1 signal intensity changes. Were the ratios that you got with this agent were they comparable to the ratios others had reported using similar techniques with other agents?

**T.D.** Yeah we tried to copy the measurement technique, the (inaudible) drawing, and the sequences and all that from the studies we know so far to make it comparable. But the direct comparison of the elevation of these ratios is quite difficult because the other papers do not show the data in such a great detail that head-to-head comparison would be possible.

**H.Y.K.** Okay. Now what about in the interval since you put this together, have you done any further analysis with some additional patients to look as two groups with the lower levels exposure didn’t actually have a statistically significant increase in the dentate nucleus signal intensity. But the problem there may have been the power, and so the question is if you have sort of added and if the lack of statistical significance persists or are they significant as well?

**T.D.** In the lower group I don’t think that we will ever reach a significant level because this is too equal to those patients who were never having gadolinium based agent. In the other two groups we saw an elevation. We saw it visually as well especially when patients approach 8 or 9 applications in the past, but I think that’s especially in the group 2 with 5 to 10 applications a matter of cohort size, of the sample size, and if we increase the sample then we’re going to reach significant values as well as I assume, but most importantly it depends also on the medical parameters in such a setting and if you do unadjusted tests for example at the level of 0.05 you will reach significance also in this group. Only in the adjusted Bonferroni-Holm corrected data set is more significant. So this is mathematical stuff and I think the problem here is rather the power of the study and the study setting and a study which is not powered to prove quality and not powered to prove the significance in such a small cohort.

**H.Y.K.** Right. Okay Dr. Tweedle, as our go-to guy, at least my go-to guy frequently, any surprises with this study? What do you see as the take-aways?

**M.F.T.** This molecule that was studied drug that was studied, is based on the same chelate agent as Magnivist uses, the gadolinium DPTA, but with an independent group that greatly increases the protein binding. So I would – if it turns out that that first group with less than five injections has, it had no signal detectable. It turns out with many studies to be of a lower order of signal intensity increase than Magnivist, I would say probably the protein binding is removing from crossing the blood brain barrier of some of the chelate agents.

**H.Y.K.** Good.

**M.F.T.** But otherwise it’s not surprising. This is a well done study and welcome.

**H.Y.K.** Great. Thank you both. Dr. Radbruch are you still paying attention?

**A.R.** Of course very much.

**H.Y.K.** Okay well you and your colleagues published a study “No Signal Intensity Increase in the Dentate Nucleus on Unenhanced T1-Weighted MR Images After More than 20 Serial Injections of Macrocyclic Gadolinium-based Contrast Agents.” So I don’t have to ask you what you found, it’s right in the title.

**A.R.** Absolutely.

**H.Y.K.** But I do have to ask you why did you decide to do this study? There’s already a lot of evidence that patients receiving macrocycles don’t show an increase in signal intensity in the dentate nucleus for example. Why did you decide to go through what was obviously a lot of work?

**A.R.** Because actually you ask patients and doctors they will tell you well like it has not been shown yet for macrocycles. And so actually like there was a very important study also published in Radiology by the Martin Prince group that assessed more than 35 injections of linears. And what we learned from this group is there’s actually not only the dentate nucleus but more structures in the brain that started to be hyper-intense the more linear agents we inject. And so there was a question for us after a very high number of injections of macrocycles will we find something and will we not? Actually our hypothesis that’s very important was driven by an idea about the physiology, about the mechanism. And so actually there were two papers published that I really want to mention here that are extremely important for the further discussion. It’s important to, it’s crucial, to actually differentiate between de-chelation and presence. I think this is something that is mixed up in the current discussion very often. There is no doubt that macrocycles are present in the brain. A different question is if there is de-chelation. So there was actually a study showing that immediately after injection, and it doesn’t matter which contrast agent, they assessed three linears and two macrocycles in the study by (inaudible) published in European Radiology. They found the same amount one day after injection of those agents for all. It doesn’t matter if linear or mac-
rrocyclics. So immediately after injection we’ve got the same amount for macrocyclics and linears for those assessed in the brain. But four weeks later, like there was a significant difference, and one study if was published two weeks ago by (inaudible) they showed that actually for the linears it was found that there were complexes found like insoluble gadolinium and gadolinium bound from (inaudible) molecules. That was not show for the macrocyclics. So actually the reason why there are differences between the macrocyclics and the linears is not the presence, it seems to be the de-chelation and our hypothesis was like we would, if that is true, like if really the de-chelation matters we would not see anything to the kinetic stability even after a very high number of injections. That is actually also what we found. If this hypothesis is correct and I would do a bold statement here to make the discussion a little bit more lively, I would project that we will never see any hyperintensities after exclusive usage of macrocyclics above the limit of the detection. But it’s a bold hypothesis, so we’ve proven this so far.

H.Y.K. I think it’s an interesting statement but it goes a bit beyond the scope of your study and I think it’s a little difficult to jump to conclusions based on the little bits of data that we have. Now why did you decide to lump all macrocyclics? They’re not all the same.

A.R. Well actually that was a matter of what was available in the department. Actually we changed from linears to macrocyclics about five years ago. We first changed to Gadavist and then to Dotarem and actually again this whole study was driven by the hypothesis that there is this (audio goes out)

H.Y.K. Dr. Radbruch I think you’re breaking up so we’re going to have to keep moving along. How did you deal with the issue of prior gadolinium based contrast MR exams? Because you had patients that had prior linear agents I believe.

A.R. Absolutely. And that’s again it’s important. Like we preformed subgroup analysis there and we published a prior study where we showed that actually if there hyperintensities that are caused by linears, in fact we found that those if we changed to macrocyclic, those might decrease over time a little bit. And so it is an important bias that you have to take into consideration as an important confounder. But the point is here and that is very important to understand; if the theory that those hyperintensities depend on gadolinium bound to macro molecules or insoluble gadolinium, like if those hyperintensities really depend on it, this will mean that a decrease could be caused by either washout or a change from the gadolinium bound to macro molecules for example gadolinium phosphate that would also cause a decrease of the signal and without that gadolinium would disappear from the tissue. So the question is which one is correct? Let me add like one consideration we also did in our study, I think one important factor is in the original study by Bob MacDonald we found a very, very strong correlation between the gadolinium that the amount of gadolinium injected and the gadolinium found in the brain. So that would at least speak against a real high washout of the de-chelated gadolinium. But again for the washout it’s important to differentiate between the de-chelated gadolinium and the chelated.

H.Y.K. Really interesting, there has been relatively little quantitative assessment of the form of the gadolinium. I mean the MacDonald study was very small. I mean I think we’re really at the beginning of our understanding, but since you raised it, one of the concerns that were raised with your study is it was also of course underpowered and the concern that the preexisting gadolinium may have obscured the deposition. So the washout of the gadolinium that had been previously given, there might be accumulation that in the ratio measurement might not appear as any change whereas in fact there might be deposition from for the macrocyclics. And this would be a general question that Dr. Evans and colleagues raised regarding the washout. We’ll get to that momentarily.

A.R. Yeah, so again we performed subgroup analysis, but I think it’s very important to understand really that we are talking about two different kinds of washouts. First of all we have to really figure out like if it’s de-chelated gadolinium or not. Dr. Evans did a great job in showing that, we will hear about this in a minute that we will find washout over time of the whole gadolinium. Actually I think what really matters is the small part of gadolinium that is released that is onto macro molecules that is according to the last published study causing the hyperintensities and that is really something we have to differentiate. We have a washout...

H.Y.K. That may be the case but we don’t – from your study we’re just looking at T1 weighted changes. We have no idea whether or not there’s the absence of T1 weight changes because gadolinium is hiding or gadolinium is there and it’s just replacing gadolinium that left. So I think your points are of interest, but it doesn’t really relate to your study. Let’s start with Dr. Evans and Dr. Tweedle, what do you think about the role of washout in the study by Dr. Radbruch and colleagues? Could there be a possibility that the washout of the linear agents is obscuring the accumulation of the macrocyclics? Dr. Evans?

P.M.E. Yeah I think that’s an important consideration. Of course we have to remember just because you don’t see hyperintensity on MR imaging doesn’t mean that gadolinium isn’t present. Dr. Radbruch raises a good point about the different forms that might be present. But it’s also the case I think that we can’t treat these agents the same. Even within the macrocyclic class there are differences between them. Though I’m aware of emerging data, for example Dr. MacDonald presented at ASNR to show that actually with one macrocyclic agent you can see gadolinium present in brain and also you can see T1 hyperintensity in a rat model and that was with Gadavist
for example. We’re also aware of other emerging data from multiple independent clinical studies which are beginning to show that with certain macrocycles again you can see T1 hyperintensity in humans. And again that was with Gadavist. And with MacDonald’s work I think that’s ongoing he’s showing differences between say Gadavist and Prohance for example. So I think to treat them all the same is not correct. We really need to understand how they’re acting within the brain. Again we’re thinking about de-chelation. You know there is work showing binding to macro molecules for example. But again that isn’t definitive proof of de-chelation, but in fact you know seeing the hyperintensities with certain macrocyclic agents does beg the question whether this is true de-chelation or some other effect. For example the chelate is self-binding to macro molecules and different interactions with tissues that are going on.

H.Y.K. Sure. Dr. Tweedle, what is your take on this stuff?

M.F.T. Well I was glad to see a non-ionic macrocycle and an ionic macrocycle having exactly the same results because it’s something that I have been pondering for some time. While it’s true that the macrocycle, the three of them, are not exactly the same, they have the same fundamental core to them which is in fact in laboratory setting responsible for their very, very slow kinetics. I mean one speciation study albeit not a strong study, did find a macrocycle left in a patient 8 years later intact. It’s not that these things will last forever, it’s just that on the full scale of all of the molecules, the differences between the macrocycles and the linear I think is a lot more than the difference among the macrocycles or among the linear.

H.Y.K. Good. Okay Dr. Evans, you and your colleagues at Amersham reported on the clearance of gadolinium from the brain without pathologic effects after repeated administration of Omniscan in healthy rats, an analytical and histological study. So can you tell us sort of what you did and what you found in your study? We’ve been sort of dancing around it a bit.

P.M.E. Yeah sure. So when embarked on this work we really wanted to understand if the gadolinium present in the brain the levels change with time, but also whether there was any potential adverse effects on (inaudible) tissue as well. We elected to use a rat model for this. Of course in pre-clinical research you can control very well confounding factors that may cause problems in clinical studies. For example you know you have full control of the type of contrast administered, you can have full control of the dose, and also the time since last exposure. So you know in full control of that we were able to study in some detail the kinetics of gadolinium in the brain with time. And the way we did this was we had animals or two different dose groups. We had a high dose group who got 20 repeat doses of and this was Gadodiamide Omniscan over a five week period, and we had a lower dose group that received 10 repeat doses over that five week period. And then what we did was two key time points and the first being one week after the last dose and the second being 20 weeks after the final dose. We sacrificed the animals by profusion fixation. That’s important because that enables you to remove any residual blood from the brain and you’re focusing on gadolinium that’s actually present in brain tissue; and also because you fixing the brain at the time of death you get very high quality tissue for morphological analysis. And so at those time points we took the brains and half of the brain by bisected midline went for ICP-MS analysis of gadolinium levels, and the other half went for a toxicologic histopathology analysis throughout the brain including several key regions. What we showed was gadolinium was of course present in the brain after administration and that was clearly dose related. So with the doubling of dose we saw an approximate of doubling the level of gad present. But one thing we noted was when you looked to the amounts retained in the whole brain of the rat compared to the total injected gadolinium, it was a very small fraction of what we actually injected. So it was equating to around one millionth of the total injected gadolinium dose. But a key finding really was as I alluded to earlier and we’ve been discussing, when you compared the levels of gadolinium at one week after last dose to 20, there was a clear reduction in the levels of gadolinium present so it reduced by approximately 50% and that’s important because it shows that much of the gadolinium there over that time frame is available for clearance in the brain over the weeks to months after exposure. And more importantly I think the toxicologic histopathology analysis showed no evidence of any cell damage or adverse tissue effects at those time points. And remember the gadolinium’s been present in the brain for up to six months at the final time point.

H.Y.K. Right now a couple of questions; did you look at the form of the gadolinium whether it was bound or unbound in your study?

P.M.E. We didn’t in the current study, no. Of course this, I’m sure everybody knows, it’s a very difficult thing to do. You know once you start extracting from tissue then there’s the danger of sort of affecting the chelate itself through the processing. But we are thinking about that moving forward. Thinking about different methods, even to look at the potentially the form in situ in the tissue, but not in the current study, no.

H.Y.K. It sounds like that’s kind of the heart of the problem we’ll get to sort of this later, but my other concern was is histopathology the optimal way to look at these kind of toxic effects because people are concerned about functional alterations, it’s a calcium competitor, it could interfere where calcium is part of a co-enzyme, or affect function of the mitochondria. There are a whole host of things that have been invoked as potentials and it would seem to me that not all of these would necessarily affect the histopathology over a 20 week period.

P.M.E. I think that’s a fair comment. You know our histopathology analysis was a first step. It’s of course the
standard approach used in safety assessment during drug development. So we thought it was important to do a full survey of the brain as we would do in that setting. But of course it’s one end point and I think you know we have ongoing work to look at multiple end points. As you said, mitochondria, ultrastructure and other aspects in the future to try and add to the weight of evidence if you’d like; it’s hard to prove a negative, but I think the more evidence we can have showing a lack of harms, the more comfortable we can be.

H.Y.K. Sure. The question that I always find (inaudible), I ask both you Dr. Evans and Dr. Tweedle, why do you think gadolinium deposition wasn’t reported in the earlier, pre-clinical tox studies that preceded the approval of these agents?

M.F.T. I doubt that it was looked for at any really low level.

H.Y.K. Okay but I would think the FDA that’s like the most important thing they want to know is that the whole thing is cleared.

M.F.T. At what level is the question? I was there and participating in development and they were quite impressed with the radioactive gadolinium studies that we did when we developed one of these agents and got down into fractions of 1% of the...

H.Y.K. Right so that goes to Dr. Evans findings that we’re sort of dealing in the millionth.

P.M.E. I think that’s true and the sensitivity of techniques now has moved on so much in the past 20 or 30 years that we’re able to detect such low levels that possibly weren’t possible during the original development of these agents.

M.F.T. But speaking of low levels we have to remember that if you see it all in the MRI you pretty much have to be in micro modar.

H.Y.K. Yep. Well sort of...

M.F.T. Considerably more than protein concentrations.

H.Y.K. Right, right. So that to me that’s the most striking thing because if it’s visible it’s just odd that we’re learning about 20 or 30 years later.

M.F.T. We may well be seeing the chelated form.

H.Y.K. I see.

M.F.T. Others could be silent.

H.Y.K. Right, right, good point. Dr. Kanal...

E.K. I think I have to listen to all this.

H.Y.K. Where are we going? What have we learned today? Where does this information fit in to the big picture of our understanding and how should people who are watching this, how should they fit this information into their fund of knowledge and potentially into their behaviors?

E.K. There are several things that I think that today’s podcast has helped bring to light and to help solidify. We’re talking about what we can see and what we can’t see and what form is it or isn’t it, so I’m going to return to my opening statement and try to reiterate that the more we learn about it the more we recognize how little we still know about exactly what’s going on, what form is it in. In fact Dr. Tweedle I understand what you just said, but I believe that many people have felt that the concentrations reported, the highest concentrations reported, by MacDonald and Kanda in their autopsies and there are only a few dozen in the world today on humans that we’ve got data on in the first place, is insufficient for us to see. Those quantities at the highest levels they’ve seen are insufficient for us to see on MRI. So based on standard T1 related imaging sequences, we have to assume they’re neither precipitin nor in their original forms but more likely in the bound to macro molecular form which means that there’s still a massive amount that we don’t understand. Dr. Evans had a tremendous point where for the past two and a half years those who take my safety courses have heard me ranting and raving that attempting to lump together linear as if they’re all the same, macrocycles as if they’re all the same, we’re doing the exact same, please pardon my bluntness, errors that the industry and the FDA has tried to do for NSF when it first came out and it didn’t work then, and the data does not support our doing so today. There seem to be substantial differences amongst the linear agents and there seem to be some substantial potential differences that we’re starting to see amongst the macrocyclic agents. But I can’t help but feel that our industry is trying to force reality to meet our theories once again instead of adjusting our theories to meet reality. In addition this entire podcast is about intracranial contrast recognizing that the intracranial concentration is a small concentration of what’s left in the bone; a small concentration of what may be present in skin. Let alone if patients have poor renal function, this is only patients with good, normal renal function. And to say that it’s one millionth the total administered dose may be appropriate for a specific location in the brain, but I’d be more interested in the number as to what’s retained in the entire body and what’s retained in a potential phosphate reservoir for example in bone is to me much more important that what might be present in just a single unilateral dentate nucleus. And finally I think it’s important that we recognize that we talked about it crossing the blood-brain barrier and the potential for doing so with protein, I think we have ample data to suggest now that there is a much, much more likely that these do not likely cross the blood-brain barrier and instead are going through the lymphatic system where the CSF pathways
and that’s hardly been discussed whatsoever in the literature but yet for years we’ve known that this pathway exists and we are able to document that it exists especially for those who for example inadvertently received intrathecal administration. So I think there’s a tremendous amount here that we still don’t know. Much of the data with tremendous respect to the individuals on this podcast, much of the data still deals with a few dozen patients at best. There’s a lot we need to understand before we make sound conclusions and broad sweeping recommendations in my opinion.

H.Y.K. Well thank you. Now we’d like to hear from the rest of our panel. I’ll go around to everyone. What are the important questions that you think we still need to answer and any thoughts about how we should go about doing this? You know sitting as an editor I’m struck by the importance, potential importance of the issue, and just kind of the exploratory nature of the data that we’re getting. It’s going to take us a while to sort this out I fear. Dr. Denecke what do you think are the most important issues we should be looking at and any suggestions as to how we might go about it?

T.D. Yeah as you said it looks like a big puzzle and the study we did was just a small contribution and I think the image of the whole puzzle when it comes together is whether there is any clinical effect. As far as we know we don’t see any, but this should be investigated even though it’s very difficult to do so.

H.Y.K. Particularly, I mean think about it, if you don’t know what you’re looking for okay and you know what you’re getting it by these you know retrospective samples that are largely confounded, it’s gonna take a long time. I just worry that we are not organized to collect enough data. I mean this is somewhere I think big data could really play a role and I’m not aware of anyone that’s marshalling the resources required to address it in that way. Dr. Radbruch what do you think we should be working on? What are the important questions that remain?

A.R. Obviously the most important question are the clinical correlates and I think it’s really very important for us as radiologists to come here together and to say to our patients that no consequences are known yet and it’s really I think personally it is extremely important to get this to rationalize, to de-emotionalize this whole debate and to really calm patients and tell them we don’t know anything. You should not be concerned at all. That’s a very important message.

H.Y.K. There is a difference between not knowing and not being concerned. You know I think it’s fair to say there has been no proof of any adverse clinical outcome related to gadolinium administration.

A.R. I totally agree.

H.Y.K. The proof doesn’t mean that it’s not an issue.

A.R. I totally agree and so that is the question like what we could do and I’m going to play devil’s advocate. Again the scientific discussion is always interesting if there are different opinions, and my personal opinion is like based on the current new studies available from the (inaudible) group that has been published one week ago. I think there is a lot of evidence that actually the hyperintensities depend on the de-chelation and there is a lot of evidence that there is in fact the major effect is a class effect and there might be still differences between the macrocyclic and linears that have to be exploited of course in future study, but I think on the data that is available right now on a pathological basis, the main differences between linears and macrocyclics and that the hyperintensities that we find in the brain actually correlate at the end of the day to the stability of what we find also in vitro. Of course there are still things that have to be enlightened. I think currently there is a lot of evidence that is fact a class effect and I don’t want to give any recommendations, but I think those are the two important points. First of all, don’t concern patients unnecessary and second of all know that there is in fact difference between de-chelation and presence, macrocyclic presence, but shouldn’t we like from toxicological point of view, be more concerned at that end of the day about de-chelation than about the presence of the chelate? So there are still a number of issues that have to be debated. Again I think we really have to, in future studies, really focus on studies that assess de-chelated gadolinium instead of mixing the chelated and de-chelated form. That’s crucial.

H.Y.K. As you were speaking I see Dr. Evans and Dr. Tweedle with varying level of grimace. So Dr. Evans you can start...

E.K. Three grimaces.

H.Y.K. Oh a third okay so we’ll have three grimaces and then we’ll sign off. What are you grimacing about Dr. Evans?

P.M.E. Oh I was just thinking I think I’m going to have to gracefully disagree with Dr. Radbruch. I think that to ascribe this simply just to de-chelation is a gross over simplification and there must be other things going on, other factors, and I think you know as the data evolves over the coming years we’re going to see you know the delineation between macrocyclics and linear is not so big and I think we’re going to understand that there’s more to this than simple de-chelation in T1 hyperintensity and presence in the brain is going to be something that is going to be seen with many if not all these agents to some extent.

H.Y.K. Dr. Tweedle?

M.F.T. Well it certainly wasn’t seen by Dr. Radbruch in a set of patients that quite a large number of macrocyclic agents. I think we need more neuro-tolerant studies in animals. You have to start in animals for this and it is well
known in animals if you use a radio tracer that between 7 and 28 days there’s not a change in washout of injected solublized free gadolinium. So I’m afraid I’m on the side of thinking that there’s going to be a large difference in clearance rate between free gadolinium and chelated gadolinium. Not that there’s no clearance of free gadolinium and so we need to understand that neuro tolerance of both chelates and the de-chelated gadolinium.

H.Y.K. Thank you.

P.M.E. I agree and if I could just chip in. So we are embarking on studies working with others actually to look at neurological functional tests in animals. I think we focused on memory cognition, the motor skills, so we are going to begin looking at that and we accept that you know there may be more subtle effects that maybe you can’t see on histopathology that really need functional tests to really look into more detail.

E.K. And if I may, two other points I just want to make sure we get in before we close, and that’s that the idea that there is less toxicity because it’s in its initial form, there certainly can be neurotoxicity for the intact chelate and perhaps less neurotoxicity for insoluble precipitate. And second of all the idea that the entire podcast is now over and we’ve never discussed the concept of relative relaxivities and that the what we’re seeing and how much of a relaxivity may be present with one agent versus another may make a difference in what you’re measuring or perceiving that your measuring let alone if there’s de-chelation and let alone if there’s reconstitution with a new macromolecule. So again trying to put too much on whether or not you do see it, especially again for Dr. Radbruch saying again all macrocycles when we know now that there are certain macrocycles that seem to behave different from others, I would like to go back and suggest that – I am not nearly as confident as others are that we can make broad statements at this stage.

H.Y.K. Well this is an exciting discussion but it will have to come to an end. You realize Dr. Kanal the president of our country decides to tweet 170 characters as a major method of communication so I worry that our listeners may have lost their ability to pay attention for this discussion. But I want to thank you all. I think it was very, very stimulating. Thank you for the papers and thank you for your interest in our journal.

Impact of in Vivo High-Field-Strength and Ultra-High-Field-Strength MR Imaging on DNA Double-Strand-Break Formation in Human Lymphocytes

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Oliver Speck, PhD • Björn Friebe, MD

Albert de Roos, MD Hello. This is Albert de Roos. I’m the Deputy Editor for Cardiac Imaging with Radiology and I’m joined today by the author of an interesting article on DNA damage from MRI studies. The article is entitled “Impact of in Vivo High-Field and Ultra-High-Field MRI on DNA Double-Strand-Break Formation in Human Lymphocytes.” The senior author is Dr. Bjorn Friebe from Magdeburg University. Welcome Dr. Friebe.

B.F. Hello. Welcome it is a pleasure to be here.

A.d.R. Thank you. So we are very interested in your article which will be published soon and to explain the background and controversies with these safety issues related to MRI and possible DNA damage, perhaps you can start to explain a little bit of background what has been published and what the controversial issues are at this moment.

B.F. Of course, sure. Our work is our topic is like part of a big discussion going on right now in MR research or better say environmental research and the question came up whether the rising exposure of electromagnetic fields like from different technical installations like mobile phones or Wi-Fi nets that are part of our daily routine life, if they can harm DNA integrity of humans and in this sense also involves MRI of course. We know that MRI is a very powerful diagnostic tool and the numbers of MRI examinations still are world-wide constantly rising and different techniques, functional anatomic imaging, whatever. Even in developing countries there are new scanners being installed and so in this context is our topic seen if the electromagnetic fields of MRI do cause damage to human DNA.

A.d.R. So and what was actually the controversial publications until now in MRI in particular? Can you explain that a little bit, the setting here?

B.F. Yeah of course. So far one has to say that there’s only very limited data available. There were some groups some years ago and they began to investigate this problem by a new, a relatively new, assay, a very sensitive cell assay, that can show double strand breaks and DNA is called the gamma H2AX assay and there was a study some years ago by a Swiss group and there was a proposal that there was a rise in double strand breaks just after cardiac MRI examination and this finding also led us to start investigating MR exposure by the detection of double strand breaks through gamma H2AX.

A.d.R. Okay so that’s the setting. There have been a number of publications in this regard as you discuss in your paper too. But what was now the actual purpose
of your study? You have experience with 7 Tesla MRI in your institution. So you went one step further to include different field strengths. What was the actual purpose of your study?

B.F. Of course. As I just said, there’s only very limited data available so and this limited data is very different also in the experimental settings. Some groups examined the effects with contrast media for example which obviously is a big issue right now at the moment, also some without, then different field strengths, different MR examination methods like cardiac imaging or whatever. And as you said here in Magdeburg we have the possibility of ultra high field MRI at 7 Tesla which we assume if there would be an effect that we could like provoke it in a stronger way because we know that in ultra high field MRI of course the energy level that deposited in the subject are much higher than lower field strengths.

A.d.R. So you did a comparison of 1.5 Tesla, 3 Tesla, and 7 Tesla?

B.F. Exactly.

A.d.R. ...in a number of subgroups of patients who underwent a clinical MR study and what were the main findings from this study? What was your main conclusion?

B.F. Our main conclusion was that under the given setting that we did and we had 4 field strength included 1, you forgot 1 Tesla, we had 1 Tesla, 1.5, 3 and 7 Tesla. Every group with contrast met the media and without contrast media our main finding was that the exposure of clinical MRI examination didn’t provoke a rise in the double strand breaks of the subjects just after the examination. We had different time points. We examined just before the examination and then immediately after the examination and then 30 minutes after the examination and we revealed no increase in DNA double strand breaks.

A.d.R. So that was your conclusion that up to 7 Tesla there were no DNA changes detectible in your setting.

B.F. Exactly.

A.d.R. But in all these articles there are little details we have to look at and I looked at some of them in your paper and I’d like to have your feedback in how to contrast them with the literature. For example, the baseline values of these changes of DNA are important to recognize there is a lot of variability as I understand it. And you corrected for this (inaudible) at baseline by normalizing the values and to look at relative changes. How important is this correction and this attention to detail of addressing the variability at baseline? Can you comment a little bit on that?

B.F. Sure. In our opinion it’s very important because as you already mentioned the baseline level on the one hand it’s not really known because it’s also part of this limited data that you cannot really tell, but like we observed it’s very low level. I mean we’re talking about a mean of foci number of gamma H2AX of around about 0.05 to let’s say 0.1 or maximum 0.2 foci per cell and there’s a big variety also in the our negative controls that are also other groups have revealed it, but the important thing would be if you are exposed under MR the relative increase of the double strand breaks. So that’s what we normalized it to the individual values of the double strand breaks and before the examination because yeah I don’t if I should continue. And the thing is also in healthy humans it is well known that you have double strand breaks and it can be influenced by a lot of other agents and it’s a stable state between induction of double strand breaks and also repair mechanism of double strand breaks. That is why there is such a large variety.

A.d.R. And actually from your control group using CT it was clear that you could measure an effect from x-ray radiation so that...

B.F. Exactly, exactly.

A.d.R. ...and the technique is working well.

B.F. Exactly and there’s another important point. You have to include control groups positive and better negative control groups to show that there’s a strong effect.

A.d.R. Yeah. So most of these studies and also your study used relatively small sample sizes. You think that’s statistically okay?

B.F. Well we all know that big sample size improves a study a lot. We have started doing this by the year of 2013 and it’s a big effort also of laboratory work. In this sense we can say that we are glad to have a fully automated, (inaudible) microscope which helped us a lot and of course a bigger sample size would be nice, but I think yeah that all groups have not bad large sizes is also a sign of the big effort the test to be taken in the laboratory.

A.d.R. So also the counting of these abnormalities is an issue and you mentioned automated digital microscopy as a valid method and I think in previous publications this assessment was mostly preformed by visual inspection.

B.F. Exactly.

A.d.R. Were you expected that will be a confounding factor for reproducibility when you take an automated method versus a visual method?

B.F. No, our system was previously, as I said in various studies, validated and it was equal in terms of the quality of the detection and helped us a lot as I said because it’s very demanding to look it up visually only. So I don’t think there would be a confounding factor.

A.d.R. So one other aspect which is quite intriguing is the time points of sampling after the MR examination, so
people with early sampling, five minutes, 30 minutes, up to one week or even one month I believe in other publications, so and sometimes there have been earlier changes; sometimes they only detect a change after two weeks or even on month. So that sounds quite controversial. Can you comment a little bit on these sampling time points and how important they are and whether we can expect a biological effect early or late and what would be reasonable in this sense?

B.F. As I said, double strand breaks are also present in healthy human beings and there’s a constant balance between the induction of the double strand breaks and repair mechanisms, and what we know is when we looked up how this method works, the gamma H2AX essay has been validated in ionizing radiation like after CT examination and there we can estimate the repair dynamics and there you can see that the highest level is like just immediately after like a half an hour after the exposure. And then you can count that 24 hours later this increase has gone so it has been repaired. So this acute or immediate exposure is the most important thing. On the other hand, the prolonged effects we did also a study on occupational MR exposure where we could see that a group with for years a constantly, repeatedly MR exposure through 7 Tesla and did not reveal an increased double strand break level. So in our opinion the most important thing would be the immediate exposure and an early time point because we cannot know what’s in much later time point would happen or what the cause there will be.

A.d.R. Okay so this is an interesting topic and you provided some interesting insight into your methods and your analysis and your results and we will see how this discussion will continue over time and I’d like to thank you for your contribution. Thank you very much.

B.F. Thank you very much. Thank you for having me.