Journal of Alzheimer's Disease 6 (2004) 673–681
IOS Press

Discussion

Vascular factors in Alzheimer's disease: Alzheimer research forum live discussion[1]

This live discussion with Jack de la Torre (*Case Western Reserve University*), *David Bennett* (*Rush University Medical Center*), *and Julie Schneider* (*Rush University Medical Center*) *was held on 21 April 2004 on the Alzheimer Research Forum. http://www.alzforum.org/res/for/journal/delatorre/default.asp*

Participants: Rob Riekse (*University of Washington*), *Geo Serban* (*Mount Sinai School of Medicine, NY*), *Julie Schneider* (*Rush University Medical Center*), *David Bennett* (*Rush Alzheimer's Disease Center, Rush University, Chicago*), *Roxana Carare-Nnadiv* (*School of Medicine, University of Southampton, U.K.*), *Mark Walker* (*Southampton University NHS Trust, U.K.*), *Mark Smith, Robert Rubey* (*Medical University of South Carolina, Charleston*), *Amy Borenstein* (*University of South Florida*), *Keith Crutcher* (*University of Cincinnati*), *Craig Atwood* (*University of Wisconsin-Madison*), *Gail Li* (*University of Washington, Seattle*), *June Kinoshita* (*Alzheimer Research Forum*), *Larry Nault* (*as listed in ARF Profiles*), *Wang Danling* (*Tongji Medical College, Wuhan, China*), *Gjumrakch* (*CWRU, Pathology*), *Jack de la Torre Jim Kallio* (*caregiver*), *Alexei Koudinov* (*Neurobiology of Lipids*).

June Kinoshita: Welcome, everyone. I am moderating today's chat. I would like to ask David and Julie to recap the question they addressed in their study.

David Bennett: We examined the extent to which cerebral infarcts and Alzheimer's disease (AD) pathology were additive to risk of dementia, or interactive-meaning the two increased risk more than the sum–or both [1].

Julie Schneider: In other words, are they additive or multiplicative?

June Kinoshita: And you found that they were additive, correct?

David Bennett: We found an additive effect, meaning infarcts and AD pathology each made a unique, and relatively independent, contribution to dementia.

Craig Atwood: Which pathology are we talking about, amyloid and infarct number and size?

Julie Schneider: We looked at number, volume, as well as location, and the findings were the same.

David Bennett: AD pathology was standard silver stained counts of neuritic plaques (NP), diffuse plaques (DP), and neurofibrillary tangles (NFT).

Gjumrakch Aliev: I do not think that these two pathologies can be separated. This is one process.

Craig Atwood: I agree with Gjumrakch.

Gjumrakch Aliev: We need to look back before any amyloid or any stroke conditions have appeared.

David Bennett: I am not sure I get Gjumrakch's point.

June Kinoshita: I think Gjumrakch is suggesting that upstream factors may result in vascular disease and AD. . . ?

[1] Note: The transcript has been edited for clarity and accuracy.

ISSN 1387-2877/04/$17.00

Jack de la Torre: I just want to say for the record, this debate or discussion (depending on one's sensitivity) should want to make people think about "what if. . . ?" which to me, are the most important two words in science. In that vein, controversy is not only good, but also desirable.

Craig Atwood: "Why" is also a good word.

Julie Schneider: I should clarify. We only looked at ischemic old macroscopic infarctions. And yes, we also looked at lacunar infarctions.

David Bennett: There was no relation between AD pathology and infarcts.

Mark Smith: So, Jack, given your hypothesis, how do you explain David's findings?

June Kinoshita: Jack, how does this finding affect your thoughts about how vascular factors and AD may be related? Certainly you provide a compelling set of correlations of overlapping pathology and risk factors [2].

Jack de la Torre: In David's study, we need to differentiate between hypoperfusion and ischemia. They looked at stroke, which is only one of the many risk factors of AD etiology.

Gjumrakch Aliev: Physicians or pathologists are able to see pathology at the later stage when clinical symptoms appear to be permanent features of these patients.

Julie Schneider: If your theory is correct, would you not expect there to be a relationship between ischemic infarctions and AD pathology.

Gjumrakch Aliev: Hypoperfusion comes first, and then ischemia or other changes occur. AD pathology and ischemia are products of hypoperfusion.

Craig Atwood: Gjumrakch, what causes the hypoperfusion, then, if it is an underlying cause of the AD and infarct pathology?

Jack de la Torre: There is a relationship between ischemia and AD, but the primary trigger begins as brain hypoperfusion and an added vascular burden such as a vascular risk factor.

David Bennett: We looked at only one aspect of the spectrum of cardiovascular disease (CVD) – old gross infarcts. These are also the ones which appear to be related to clinical disease.

Amy Borenstein: How do white matter hyperintensities figure in here? (Subclinical infarcts?).

Roxana Carare-Nnadi: Did you assess the degree of amyloid angiopathy?

June Kinoshita: Let us let David and Julie answer Amy's question, and also Roxana's.

David Bennett: Good question. We did not measure white matter changes that were not infarcts.

Julie Schneider: We did not look at white matter hyperintensities specifically. Subclinical infarctions were not as strongly related to clinical disease, as shown in an earlier manuscript. No, we did not assess amyloid angiopathy specifically.

Mark Walker: If macroscopic infarct was the only aspect of CVD entered into the analysis, then perhaps results would have been considerably different if other variables (imaging, histology) were added into the analysis.

Amy Borenstein: The Nun Study found that subclinical infarctions interacted with AD pathology to cause the dementing syndrome.

Julie Schneider: We did look at microscopic infarctions and there was also no interaction with AD pathology.

David Bennett: We were unable to replicate the findings from the Nun Study.

June Kinoshita: Are there any other questions about the pathology findings from David and Julie's paper? Let us wrap up this topic before we move on to the next.

Craig Atwood: Did you look in the posterior cingulate area?

Julie Schneider: All areas were evaluated for macroscopic infarctions, including posterior cingulate.

Craig Atwood: What were the results for the posterior cingulate? Was there a comparable pathology with, say, the areas of the entorhinal cortex?

David Bennett: We did not assess posterior cingulate in the prior study. But that is an important area, and we are doing it now in a follow-up study.

Jack de la Torre: Risk factors for brain vascular disease, such as diabetes, atherosclerosis, hypercholesterolemia, coronary artery disease, hypertension, stroke, hyperhomocysteinemia, and aging are also risk factors for AD. Therefore, factors that predispose to cerebrovascular and cardiac diseases also increase the risk for AD.

David Bennett: Jack, we agree. The question is mechanism. It could be that they cause infarctions, which add to risk of dementia.

Mark Smith: Is congestive heart disease, which likely causes hypoperfusion, a risk for AD?

Jack de la Torre: Yes.

June Kinoshita: David, great segue into the mechanism topic. So, perhaps we can dig deeper into hypoperfusion.

Jack de la Torre: Remember, aging already involves brain hypoperfusion.

Amy Borenstein: In my view, vascular risk factors can show up as risk factors for AD because they "bring out" the dementia when AD pathology is also present. I think this is what David and Julie's paper says, and I agree with it.

Jack de la Torre: Certainly not. Let me explain. Many vascular risk factors already exist much before any AD symptoms or even mild cognitive impairment (MCI); atherosclerosis, head trauma, smoking, hypertension, cardiac disease, and diabetes are just a few of these risk factors that can be present decades before AD. For example, epidemiological data including the Rotterdam Study, the Kungsholmen project, EURODEM, the Honolulu-Asia study, and others strongly support a vascular role in precipitating AD. Also, the Whitehall Study [3], showed in 1,600 subjects that vascular disease predicts poor cognitive function; in addition, brain blood flow studies can predict AD at the MCI stage and PET studies even prior to MCI. Drugs that mildly help AD symptoms all improve CBF mildly. This is only a brief explanation, because I and others have written extensively on this subject.

Julie Schneider: But if these increase risk for infarctions and infarctions decrease the threshold for dementia, this may be the mechanism for increased risk. I think that the epidemiologic studies support either mechanism.

Jack de la Torre: Coronary artery by-pass grafts (CABG) may be another important risk factor that has not been investigated fully.

Gjumrakch Aliev: Jack, I think we need to add one more issue. Vascular lesions induced by chronic hypoperfusion appear to be the primary target for AD.

June Kinoshita: Jack, do you think that hypoperfusion is the point of convergence, where these multiple and diverse risk factors meet, and from there events are set in motion that lead to AD? Or does one have to go further upstream?

Amy Borenstein: The epidemiological data show that vascular factors lead to an earlier presentation of dementia/AD. We all seem to agree that vascular factors are important in increasing risk for AD, but we are discussing whether there is a direct effect or whether vascular factors are "enabling" factors for bringing out the dementia.

Julie Schneider: Again, CABG is probably related to subclinical infarction, which decreases the threshold for expressing dementia.

Roxana Carare-Nnadi: In the review published in Lancet Neurology [2], the vascular hypothesis (hypoperfusion leading to neuroglial energy crisis) is a clear explanation for the neurodegeneration, but how does hypoperfusion lead to/explain amyloid accumulation?

Jack de la Torre: When you combine aging (chronic brain hypoperfusion) with a vascular risk factor (more hypoperfusion), you get more reduced cerebral blood flow; eventually this turns sour for the subject because the neurons develop a metabolic energy crisis.

Craig Atwood: Roxana, hypoperfusion will lead to death of neurons and amyloid-β production. Amyloid is a marker of degeneration, and unlikely the primary cause.

Gjumrakch Aliev: It has been clearly shown that after heart transplantation, patients always get dementia.

Amy Borenstein: Gjumrakch, "always" is a strong word.

David Bennett: If infarcts and AD pathology had a common etiopathogenesis, we would expect them to be related, but they were not.

Mark Smith: Anyone buy into the coincidence that neurons and cardiac cells are postmitotic? Mechanism?

Jack de la Torre: Animal studies show induced ischemia increases amyloid deposition.

Gjumrakch Aliev: Amyloid can be accumulated after any type of damage. Ischemia is only one factor inducing amyloid deposition.

Alexei Koudinov: I agree with Gjumrakch.

Gjumrakch Aliev: Thanks, Alexei. I think we need to focus on the reasons, not the consequences of the brain lesions or damage.

Craig Atwood: Gjumrakch makes a good point; any degeneration will result in amyloid-β generation and deposition (e.g., head injury or toxicity in vitro).

Julie Schneider: Hippocampal sclerosis is a common age-related pathology seen with AD and vascular dementia. Perhaps this is another mechanism by which vascular risk factors increase the risk of dementia.

David Bennett: I agree that we need to do antibody-specific staining for amyloid (and tau) before discounting the association. We are doing that.

June Kinoshita: Will you be ready to present the results in Philadelphia, David?

David Bennett: June, we are getting close, with only a third of subjects having infarcts. We need amyloid and tau data on at least 150 cases – a time-consuming endeavor.

Julie Schneider: The hypoperfusion is in the regions that are most susceptible to AD pathology, but not a vascular territory.

June Kinoshita: Julie. Can you clarify what you mean by "vascular territory"?

Julie Schneider: Vessels that supply the brain have specific territories; AD pathology does not follow these territories or even the watershed areas.

Jack de la Torre: Also, asymptomatic patients at risk for AD exhibit marked alterations in cerebral perfusion, as assessed by PET, SPECT, or MRI. Because hypoperfusion precedes the onset of cognitive decline; it cannot be attributed to the brain dysfunction produced by the disease. There is intriguing evidence that Aβ production in AD may be a neuroprotective reaction against some stress: oxidative, trauma, ischemia, etc. Any comments?

Mark Smith: Jack, see Free Radic Biol Med, "Tau and Amyloid-β serve antioxidant function." [4].

Jack de la Torre: I saw it.

Craig Atwood: Jack, unlikely to be oxidative stress (unpublished results). When a cell undergoes apoptosis, it produces amyloid-β, whether it has been induced to die via overwhelming oxidative stress or other agents.

Gjumrakch Aliev: Craig, a large neuron does not have a chance to die via apoptosis, and this is already shown in a different model, including human study.

Jack de la Torre: Craig, you may be right.

Alexei Koudinov: To Dr. de la Torre's point, I would add that Aβ is also related to lipid (particularly cholesterol) metabolism, and in synaptic function.

Gjumrakch Aliev: Amyloid is the product of brain lesions.

Julie Schneider: Gjumrakch, what brain lesions?

Craig Atwood: Gjumrakch, then where are they going?

June Kinoshita: Gjumrakch, what is the citation on that?

Gjumrakch Aliev: June, the citation is in J. Neuroscience, I think, 2001. The study was done in a gerbil model of brain ischemia. In addition, we did not find any apoptotic neuron in human AD brain biopsy as well as postmortem tissue. Large neuron can be compared to an airplane. They do not have chance to die slowly.

Craig Atwood: Gjumrakch, did you do any gerbil studies?

Jack de la Torre: Let me also say that no animal data that examines a disease complex, no matter how brilliant the experiment, can ever substitute for relevant human data. This is axiomatic and undisputable.

Roxana Carare-Nnadi: However, animal studies using intracerebrally injected tracers show deposition of these tracers in perivascular spaces in a manner/pattern comparable to cerebral amyloid angiopathy (CAA). Would you consider Aβ accumulation a result of failure of the physiologic mechanism of interstitial fluid (ISF) drainage?

Julie Schneider: Jack, there are other diseases that cause chronic cerebral ischemia, e.g., Moyamoya, but do not predispose to AD. Explanation?

Jack de la Torre: Ischemia has to affect the right place and age. Moyamoya affects usually children who develop ischemic or hemorrhagic stroke often in pia mater vessels. That is why some strokes in non-cognitive brain regions, even in the elderly, do not lead necessarily to AD.

Mark Smith: Craig, neurons die but not by apoptosis (we discussed this in Science/Nature several years ago [5,6].

Craig Atwood: Okay, apoptosis was the wrong word. Neuronal death, then.

Mark Smith: Then yes, neurons do die!

Julie Schneider: Jack, so, your suggestion is that it has to be global rather than focal ischemia?

Jack de la Torre: Julie, usually it is global hypoperfusion, ischemia may not be a proper description because it can involve focal, non-vital brain regions! Silent stroke (which some of us here may have) affects millions in the world, and they are at risk for AD. But, some silent strokes never lead to AD. Any comments?

Julie Schneider: Again, our data suggests an additive effect of all types of infarctions. No interaction with AD pathology.

Amy Borenstein: Jack, AD is a threshold disease, and silent/overt strokes, in addition to other vascular risk factors, increase the slope for earlier presentation of dementia/AD.

David Bennett: Jack, we did not find an association between subclinical infarcts and dementia. However, we might still see it with a much larger sample size.

Jack de la Torre: Remember, ischemia is measurable (OEF, CMRO2, etc.), but hypoperfusion may go unnoticed for a long time. Also, mild or moderate hypoperfusion is usually not associated with severe metabolic changes such as influx of calcium and sodium ions and prolonged decreases in ATP and increases in lactate levels, that and neuronal damage may come much later.

Gjumrakch Aliev: Jack, hypoperfusion can occur any minute in any brain area. Often, the process can be global such as head trauma or total ischemia or hypoxia (or correctly, anoxia).

Jack de la Torre: I agree.

Julie Schneider: If indeed there is hypoperfusion causing AD, would you not expect the watershed regions and selective vulnerable neurons to be the only ones involved in AD pathology, rather than the more global changes we see?

June Kinoshita: Do imaging studies support the idea of widespread or more global hypoperfusion in people at risk of AD? I am familiar only with studies showing hypoperfusion in focal regions.

Gjumrakch Aliev: June, please do not forget about the technical difficulty of the technique and the likelihood of detecting measurable changes.

Julie Schneider: June, I agree. That is an important point. There is no evidence of global ischemia on these scans.

Gjumrakch Aliev: Julie, what is the percentage of ischemia that can be detected by scan?

Julie Schneider: Gjumrakch, we do not know the percentages.

Craig Atwood: Julie, depends on the diameter of the vessels, and I would suggest that those in hippocampus are smaller than elsewhere in less affected regions of the brain.

Jack de la Torre: Watershed regions are seen in stroke, not usually with hypoperfusion.

Roxana Carare-Nnadi: Watershed regions would not be the only ones involved; changes would be noticed in proximal arterial territories (cortical, leptomeningeal).

Mark Smith: Apolipoprotein E is a risk factor for vascular changes but is this only in whites? Since there is a difference in races and in AD susceptibility?

Jack de la Torre: Apolipoprotein E is a risk factor for cardiac and cardiovascular diseases.

Mark Smith: In all races?

Jack de la Torre: Hypometabolism/hypoperfusion is both cortical as well as subcortical.

Craig Atwood: David, so with both subclinical infarcts and AD, you might expect amyloid deposition if it is a response to neurodegeneration?

David Bennett: Craig, I am not sure I understand the question. Our study may not have had sufficient power to detect an association with subclinical infarcts. Alternatively, we might yet get a different answer with amyloid immunostaining than with silver staining techniques. Is that what you were looking for?

Craig Atwood: David, what is the amyloid load with infarcts versus the AD brain? When we say pathology for amyloid, are we really just saying neurodegeneration (cell death)?

David Bennett: Craig, we are measuring amyloid load, and counting neurons, but I do not have the answer yet.

Mark Smith: Craig, amyloid does not really relate to neurodegeneration.

Gjumrakch Aliev: Craig, measurement of amyloid load and/or counting neurons has nothing to do with AD etiopathology.

Craig Atwood: Mark, has anyone looked at neuron loss stereotaxically and measured amyloid load?

Mark Smith: Not exactly, but there is little to no neuronal loss in normal aging by stereotaxic measures, yet there is often amyloid!

Gjumrakch Aliev: Craig, many things need to be done in science. You can also study stereotaxicity of glial cells. Because this kind of study has not been performed.

Craig Atwood: I agree cognition does not correlate with amyloid load, but I have not seen the normal aging data. Besides, how do you know localized regions have not lost neurons, or deposited amyloid as a response to their reentry into the cell cycle?

David Bennett: Craig, amyloid is related to cognition. But you lose the effect after controlling for tau [7]. We think that means that tau mediates the effect of amyloid on cognition, but not that it is unimportant.

Jack de la Torre: The notion that presence of cerebrovascular disease is an exclusion criterion for AD diagnosis has stunted any real progress in AD research. Any comments?

David Bennett: I agree with Jack's statement above. The field would be much better not excluding coexisting diseases from the diagnosis of AD.

Mark Smith: Depends whether you are a lumper or a splitter, I guess.

Julie Schneider: Agree completely. Very often, it is a mixed pathology. We need to be looking at both pathologies.

Amy Borenstein: You can still be diagnosed with possible AD (by National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria) and included these in analyses.

Julie Schneider: By splitting, you are excluding about one-third of real persons with AD.

Amy Borenstein: I agree with Julie.

June Kinoshita: Jack, Julie, and David, should there be a revision in the diagnostic criteria?

Jack de la Torre: Absolutely!

Mark Smith: I agree, but since one-third normal aged have senile plaques (SP)/neurofibrillary tangles (NFT) for diagnosis of AD, then CVD may simply fool

the pathologist into diagnosing the dementia to mixed AD/vascular dementia (VaD).

Jack de la Torre: AD should be regarded as a "vasocognopathy" (a new term I have coined, see Neurol Res July, 2004 issue). The evidence for AD as a vascular disorder is so powerful that we need to revise our thinking for the last 25 years.

Amy Borenstein: Jack, do you then think that there is no "pure" AD?

Jack de la Torre: Amy, there is probably no pure AD or VaD.

Julie Schneider: I am not sure I agree at this point that AD is a vascular disease. I think we might be talking about two very common pathologies that often coexist in the aging brain and contribute to dementia.

Amy Borenstein: I disagree; what about young cases who do not have a vascular contribution?

Julie Schneider: Yes, agree. I do not have numbers, but my experience is that the younger cases and hereditary cases are more often pure than the older cases.

Craig Atwood: Sounds like AD is just "aging."

Jack de la Torre: There will be a special issue of Neurological Research in July 2004 discussing the role of vascular factors in AD and VaD. Hopefully, the issue will be available at the Philadelphia meeting.

Amy Borenstein: Maybe we should study "dementia" instead of NINCDS (National Institute of Neurological and Communicative Diseases) criteria?

Julie Schneider: Amy, yes, I think that often there are combined pathologies in the real world causing dementia. Not only infarctions, but also Lewy body disease, etc.

Amy Borenstein: Combined pathology is common as age increases.

Jim Kallio: How does ischemia from head trauma fit into this picture overall.

Jack de la Torre: Head injury (severe) is known to reduce brain blood flow for long time periods.

June Kinoshita: Jack, how long? Months? Years?

Jack de la Torre: June, years, but Aβ is sometimes seen right after head trauma.

Mark Smith: Jack, but then it disappears.

Alexei Koudinov: Jack, Mark, the disappearance is another good proof of a transitory and/or compensatory nature of amyloid deposits.

Gjumrakch Aliev: I agree with Alexei. Amyloid is compensatory reaction of the brain tissue to the action of injury stimuli. In addition, amyloid can be produced in any brain cells.

Amy Borenstein: In studies about 15–20 years ago, it was shown that head trauma results in Aβ deposition [8].

Julie Schneider: Dementia pugilistica shows diffuse plaques and sometimes some tangles, but not typical AD pathology.

Gail Li: Besides aging, apolipoprotein E4 allele is another risk factor for AD found in epidemiological studies consistently. What is the role of apolipoprotein E genotype in the hypoperfusion theory?

Jack de la Torre: As I said, apolipoprotein E4 is the precursor of reduced cerebral blood flow (CBF).

Julie Schneider: I am presenting data at the AAN next week showing that apolipoprotein E4 increases odds of cerebral infarction.

Gjumrakch Aliev: Gail, hypoperfusion can be induced by any factor. Genetic or exogenous!

Gail Li: Do we know the pathway between reduced CBF and apolipoprotein E4?

Mark Smith: Jack, do patients with Down's syndrome who go on to develop AD pathology show hypoperfusion?

Gjumrakch Aliev: Mark, yes! Down's syndrome shows clear hypoperfusion induced by genetic abnormality.

Jack de la Torre: Mark, it has been shown that Down's patients develop blood flow and capillary problems before senile plaques [9].

June Kinoshita: Mark, that reminds me of an interesting factoid I learned from Judah Folkman. People with Down's syndrome never develop solid tumor, and he thinks this may be due to the overexpression of an antiangiogenic factor on Chr 21.

Mark Smith: June, interesting!

Gjumrakch Aliev: June, regarding solid tumor. Usually Down's patients do not have a long enough life to develop solid tumor.

June Kinoshita: We have 10 minutes left of our allotted time. I would like to ask people to propose productive future studies to address the role of vascular factors in AD. Can we start with Jack, David, and Julie, and then open the floor to the audience?

Jack de la Torre: The difference between AD and VaD in my opinion is either slow or sudden CBF reduction.

David Bennett: Our plan is to see if vascular factors related to dementia (e.g., diabetes, hypertension) do so through an association with infarcts or with AD pathology.

Roxana Carare-Nnadi: Aging is associated with arteriosclerosis (and hypoperfusion). Vascular changes present especially at capillary level (basement membrane changes) and change the physiological interactions of soluble Aβ with basement membrane components; this might promote the formation and deposition of fibrillar Aβ?

Julie Schneider: June, I think that more work looking at the brain changes associated with AD such as small vessel disease (lipohyalinosis), white matter changes, amyloid angiopathy, and hippocampal sclerosis, and whether these pathologies merely accompany AD pathology or interact with AD pathology and cause a multiplicative effect, may be of interest.

Roxana Carare-Nnadi: Absolutely agree.

Jack de la Torre: To get back to the hypoperfusion story in AD, can we say that it would be absurd to wave off the dozens of epidemiologic studies showing that vascular-related risk factors increase the chance of developing AD? It is like saying that cigarette smoking and lung cancer, or heart disease, are associated by coincidence.

Amy Borenstein: Jack, of course those epidemiological studies should not be dismissed! It is their interpretation. . .

Gjumrakch Aliev: Jack, we need to use strong words. Vessel hypoperfusion is not risk, but primary factor for the development of any brain pathology the consequence of this damage is a cognitive problem and future amyloid, etc.

Amy Borenstein: Jack, but they can all be interpreted as contributing to lowering threshold.

Craig Atwood: Jack, the same can be said for reproductive hormones given the large number of epidemiological studies.

Amy Borenstein: To follow up on David's point: I think you have to have the whole causal mechanism to study; a good handle on risk factors (measurement and timing); clinical diagnosis; and pathology on almost everyone. Very hard to do. The Rotterdam Study and Nun Study can do this.

Julie Schneider: Agree. The studies that David mentioned that our group is doing may help to sort out the mechanism by which these risk factors work.

Jack de la Torre: But besides the epidemiological studies supporting a vascular role for AD, there are many other studies, neuroimaging, pharmacotherapy, etc.

Jim Kallio: So how do the results from the WHI study fit into this picture, too? Although the results seem to be yo-yoing around now.

Craig Atwood: WHI studies were performed with medroxyprogesterone and conjugated equine estrogens, not 17β-estradiol and progesterone, so interpretation is difficult.

Jack de la Torre: We also need to look at vascular nitric oxide in AD, a sneaky molecule!

June Kinoshita: In our final few minutes, could we discuss the implications for treatment, identifying people at risk of AD, etc.?

Craig Atwood: Does the Spark's Lipitor study excite anyone?

Julie Schneider: June, we (clinicians) need to be paying more attention to vascular risk factors and vascular health for decreasing the risk of AD, since AD is often mixed and can be precipitated by cerebral infarction.

Jack de la Torre: We need above all to give AD patients a chance of hope for the future; present AD research into amyloid is doing little in this regard.

Gjumrakch Aliev: Julie, vessel angiopathy and AD are not mixed. First, changes occur in vessels. Amyloid is a consequence of a vessel problem.

Craig Atwood: Lipitor and halting cognitive decline. Does cholesterol have anything to do with vasculature?

Jim Kallio: I would think cholesterol has vast implications on that.

Rob Riekse: Any other thoughts with cholesterol and AD?

Alexei Koudinov: I think that lipid metabolism and oxidative stress cascade could provide a pathogenetic explanation for the vascular factors in AD.

Wang Danling: Tau protein is more related to dementia than amyloid; why not discuss the possible relationship between tau and vascular factor.

David Bennett: We are looking at tau, too.

Alexei Koudinov: Addressing tau and Aβ interrelation, coined above. I think that both can serve independent compensatory function that we started to discuss three years ago [10], Aβ may affect lipid metabolism, or cholesterol uptake, for example, while tau changes (that I hardly can call pathological, as hyperphosphorylation happens at certain ontogenesis stages and then is gone) may help to rearrange neuronal cytoskeleton to help restore neurotransmission, for example. Such looks provide a clue for the explanation of the overlap of neurodegeneration features across different neurodegenerative diseases (in Parkinson's, for example).

June Kinoshita: Our time is up. Thank you everyone for attending today.

References

[1] J.A. Schneider, R.S. Wilson, J.L. Bienias, D.A. Evans and D.A. Bennett, Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology, *Neurology* **62** (2004), 1148–1155.

[2] J.C. de la Torre, Is Alzheimer's disease a neurodegenerative or a vascular disorder? *Data, dogma, and dialectics. Lancet Neurol* **3** (2004), 184–190.

[3] A. Singh-Manoux, A.R. Britton and M. Marmot, Vascular disease and cognitive function: evidence from the Whitehall II Study, *J Am Geriatr Soc* **51** (2003), 1445–1450.

[4] M.A. Smith, G. Casadesus, J.A. Joseph and G. Perry, Amyloid-beta and tau serve antioxidant functions in the aging and Alzheimer brain, *Free Radic Biol Med* **33** (2002), 1194–1199.

[5] G. Perry, A. Nunomura, P. Lucassen, H. Lassmann and M.A. Smith, Apoptosis and Alzheimer's disease, *Science* **282** (1998), 1268–1269.

[6] G. Perry, A. Nunomura and M.A. Smith, A suicide note from Alzheimer disease neurons? *Nat Med* **4** (1998), 897–898.

[7] D.A. Bennett, J.A. Schneider, R.S. Wilson, J.L. Bienias and S.E. Arnold, Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function, *Arch Neurol* **61** (2004), 378–384.

[8] D.I. Graham, S.M. Gentleman, A. Lynch and G.W. Roberts, Distribution of beta-amyloid protein in the brain following severe head injury, *Neuropathol Appl Neurobiol* **21** (1995), 27–34.

[9] L. Buée, P.R. Hof and A. Delacourte, Brain microvascular changes in Alzheimer's disease and other dementias, *Ann NY Acad Sci* **826** (1997), 7–24.

[10] A.R. Koudinov and N.V. Koudinova, Essential role for cholesterol in synaptic plasticity and neuronal degeneration, *FASEB J* **15** (2001), 1858–1860.