[MUSIC PLAYING]

DANIEL VARON: It's very nice to be here. So I'm going to talk about LATE, like Ellen mentioned. And this is a newly identified ideology of dementia.

And basically, what it stands for is Limbic-predominant Age-related TDP-43 Encephalopathy. And basically, the name kind of tells you what this is about. It's a neurocognitive disorder that's related to TDP-43. It's usually accumulating in the limbic regions and seems to be most prominent in people that are older. And it causes a progressive dementia.

So in order to understand this better, let's look at a clinical case. And then we'll talk about LATE a little bit more. So this is a patient who's 83, presented to the memory disorder center with her family. Four years before, she had started to have some memory problems.

She was writing notes, leaving notes throughout her house to try to remind herself of things. And the family noticed that this was getting progressively worse. When asked if there was a precipitating factor, they actually said that she had some stroke-like symptoms three years before, with some facial asymmetry and some difficulties moving left upper extremity.

Those symptoms resolved after three days. And actually, she had no new cognitive deficits after the stroke-like symptoms. But they did notice over time, she started to have more difficulty with orientation, would have a hard time getting around familiar places.

And then eventually, she had to move into a personal care home. And then gradually, she seemed to be worse in terms of her memory, repeating the same stories, asking the same questions, and then eventually, requiring assistance with most instrumental activities of daily living. Although she was still able to do basic activities of daily living at the time she presented to the clinic.

In terms of her past history, the main things were hypothyroidism, this history of possible stroke that I mentioned earlier. She had an MI and vitamin B12 deficiency. She was a widow. She was widowed, and she had worked as a leasing officer until age 65. She was a smoker but had not smoked for a long time before she presented to the clinic.

And her neuro exam was pretty unremarkable. She had a little bit of reflexes on the left side and a little bit mild decreasing arm swing on the left arm. But other than that, nothing else in the neuro exam. But she did have an abnormal cognitive testing. She had a Mini-Mental of 19 out of 30 and a clinical dementia rating score of 1, which would be consistent with a mild dementia, although given that MMSE, probably closer to moderate dementia.

And this is her MMSE over time. And you can see here that she had initially 19. The second year that she was evaluated in the memory disorder clinic, she had 21. And then at year three, back to 19 and eventually to 16.

So she gradually got worse over time. And by the time she got to a year four, her CDR score was 2, clearly a moderate dementia. So clinically, she was given a diagnosis of probable Alzheimer's disease. Which makes sense, obviously, because she's an older patient that presents with progressive memory loss. And so that's what you would give clinically.

And then she actually donated her brain. So she went for autopsy. And these are the neuropathological diagnoses. So you can see there that she was diagnosed or given a diagnosis of probable Alzheimer's disease in the neuropathology but also mesial temporal sclerosis, dementia with Lewy bodies, and amyloid angiopathy.

Now, there's a couple of things that are important about this report. And one is that there was no evidence of a stroke. Two, when you read the actual report, the neuropathology said that the AD changes were mild. But because of the presence of the mild temporal sclerosis, the idea was that perhaps that was related to Alzheimer's disease. And so the diagnosis of probable Alzheimer's disease was given.

Also, the Lewy bodies were restricted to the limbic regions. And it was hard to see whether or not that was relevant in terms of the clinical presentation she had when she was alive. So those things we have to keep in mind, but we'll come back to this. And let's talk a little bit about LATE, and then we'll revisit these neuropathological diagnoses.

So LATE is a proteinopathy. Basically, we treat a lot of neurodegenerative disorders that are proteinopathies. Alzheimer's disease is one of them, CJD is another. And depending on what protein aggregates, then you have the disorder.

So all of these are diseases that we talk about often, Pick's disease is one of them, PSP, corticobasal degeneration. CTE or chronic thrombotic encephalopathy is one that we've been talking about more in recent years. And then these synucleinopathies, like the DLB, Parkinson's disease, or multiple systems atrophy, are also proteinopathies. But more recently, TDP-43 was described in FTLD, frontotemporal lobar degeneration, and amyotrophic lateral sclerosis. So these became part of the picture of the proteinopathies and the neurodegenerative disorders.

So TDP-43 is a normal nuclear protein that you see in multiple cell lines. But when it becomes pathological, it's translocated from the nucleus to the cytoplasm, and that's when it becomes pathological. And it's usually involved in gene expression. It binds to DNA and RNA.

And already in 1994, Dennis Dickson had described these cases of people that had a hippocampal sclerosis that looked like Alzheimer's disease. But when you would look at the pathology, they didn't have AD pathology. And then in 2006, TDP-43 was discovered to be a major component of neuronal inclusions in ALS and frontotemporal lobar degeneration.

But then people started to describe the presence of TDP-43 inclusions in other conditions. And so, for instance, things like Alzheimer's disease, argyrophilic grain disease, and hippocampal sclerosis with amnestic syndrome were all characterized by the presence of TDP-43 as well. So it seemed like the TDP-43 was present in other conditions as well.

Also, there is a subgroup of patients that seem to have AD-- they present with amnestic disorder, and they have hippocampal atrophy. But again, they don't have amyloid deposition. And they have been characterized or labeled as SNAP, Suspected Non-AD Pathology.

So those people, along with the people that Dennis Dickson and similar cases described in the past, are probably people that had TDP-43 pathologies. So these are, again, people that present with an amnestic syndrome. When you look at the pathology, they don't have AD pathology. So that's important to keep in mind.

So in order to characterize those patients and to kind of give them a name, a consensus group was created. And they actually published this article in *Brain* last year. And they coined the term LATE. And as I was mentioning before, in these cases, TDP-43 seems to be most prominently deposited in the limbic system. So what they basically described in their paper is that LATE is often seen in older patients with amnestic disorders.

The features of the condition are very similar to what you would see in Alzheimer's disease. But the TDP-43 inclusions are distinct from what you would see in frontotemporal lobar degeneration, which, again, is another condition where you would see TDP-43. And often, hippocampal sclerosis can be present, although that's not necessary or sufficient to make the diagnosis of LATE.

So how common is this condition? So if you look at the Rush Memory and Aging Project and the Religious Orders Study-- which has been done for a very long period of time, and they have a lot of brains that have come to autopsy-- half their participants have TDP-43 pathology. And actually, 37% have both TDP and AD pathology. So that's a large number of patients that have TDP-43 pathology.

If you look at the people that have AD-type dementia, meaning people that present with something that looks like AD and were given a diagnosis of AD while they were still alive, actually, the number of people that have TDP-43 pathology is more than 50%. You can see there the area in purple. Those are the people that have AD pathology and TDP-43 pathology.

But more interestingly, there's this blue area. Those are the people that were given a diagnosis of AD, and did not have any AD pathology but had TDP-43 pathologies. So those are very important. And you can see these are patients who are fairly old.

And so when you look at this, people that are diagnosed with AD, probably 15% to 20%, when they're diagnosed clinically with AD, probably are explained by LATE. So there's a large chunk of people that do not have Alzheimer's disease but actually have LATE. And these are people that are older people that are close to their 90s, people that are over 85 generally. So based on that, the impact of LATE is probably half of the impact of Alzheimer's disease in older people and probably equal to the impact of all vascular neuropathologies combined. So that's an important condition that had not been described in the past.

And the clinical manifestations of this, as I mentioned before, are very similar to what you would see in Alzheimer's disease, with episodic memory in older people. When TDP-43 pathology presents by itself, without the presence of AD pathology, the memory loss is more gradual. But when it's combined with AD pathology, the symptoms are worse than what you would see in AD alone. So people tend to progress a little bit more quickly.

It tends to progress in a specific pattern or a specific fashion. So it usually starts in the amygdala in stage 1. And then it involves the hippocampus and entorhinal cortex, and eventually, the neocortex by stage 3.

So it progressively involves other areas of the brain. So people can have other cognitive alterations aside from memory. But initially, memory is the main cognitive alteration.

So how do you distinguish LATE from AD? And that's the real question. And it's very hard to do that.

Ultimately, if you look at a group of people with LATE in the neuropathological diagnosis, you can see there that people with LATE, even at early stages, they have MCI or dementia. So even in stage 1, more than half already have MCI or dementia. And by stage 3, most of them have a neurocognitive disorder.

But a lot of them are very old, and they progressively get worse on the global cognitive tests. And episodic memory gets worse as well as the disease progresses. But all of this is very typical of Alzheimer's disease as well. So it's very hard to distinguish that from a patient with Alzheimer's disease.

The consensus paper says, well, maybe memory tests could be a way to distinguish them from people with Alzheimer's disease if there's no evidence of alterations in verbal fluency. So they suggest that hippocampal function would be important, obviously, in memory tasks. And neocortical gray matter volumes would be important in verbal fluency tasks.

So if you have a patient that presents with word recall deficits or primarily memory deficits without alterations in verbal fluency, maybe those patients would correspond to patients with LATE. But that could also be a patient with Alzheimer's disease. And in general, it would be very hard to distinguish someone in a clinic based just on the neuropsych testing.

Now, if you were to look at biomarkers-- and the A/T/N system is used to classify people with AD. And basically, you look for amyloid deposition, tau, and neurodegeneration. If you were to have these biomarkers, then maybe you could potentially identify some patients that might have LATE.

And so you can see two examples here of patients with specific profiles. This is an 86-year-old female with progressive amnestic dementia. And you see they don't have amyloid.

This person doesn't have amyloid, no tau. But neurodegeneration is present because of hippocampal atrophy. So this person could have LATE. So there's no evidence of biomarkers for Alzheimer's disease, but there's evidence of neurodegeneration.

This is another case, where LATE could be a part of the picture. So this person has amyloid but no tau and evidence of neurodegeneration. Again, this is the patient that potentially could have LATE as part of the picture.

So if we revisit this case that I presented earlier, this 83-year-old with progressive memory loss, you can see there that the initial diagnoses, again, were mesial temporal sclerosis, probable Alzheimer's disease. And when the pathologists looked at this, now with the ability to stain for TDP-43, the diagnosis changed. And so this patient actually had LATE, stage 2 to 3, with hippocampal sclerosis.

And when looking at the Lewy body-related pathology, it seemed to be limbic but not necessarily enough to explain the cognitive deficits. Same with the Alzheimer's disease pathology. It was low-level and not necessarily enough to explain the patient's deficits. So it's important because evidently, over time, our diagnosis has changed. And some of these patients that we initially thought were Alzheimer's disease have a different condition.

So in summary, LATE is a condition that is present often in older patients with amnestic disorders. The TDP-43 is the main protein that is driving the pathology. But the distribution of the inclusions is different from what you would see in FTLD.

And it usually progresses from the amygdala to the entorhinal cortex, to the hippocampus, and then to the neocortex. And it can be associated with hippocampal sclerosis. But again, hippocampal sclerosis is not necessary or sufficient to make the diagnosis. And the clinical features are very similar to those of Alzheimer's disease. And it would be very difficult to distinguish from Alzheimer's disease unless you have biomarkers.

So in the future, if we have biomarkers for LATE, or if the biomarkers that are currently available for Alzheimer's disease are easily used in the clinical setting, then we might be able to identify some patients that potentially have LATE. And that will be important in the future when you have targeted treatments for specific conditions. So with that, I will end. Thank you.