

[MUSIC PLAYING]

ERIC RODRIGUEZ: Hello. This is Eric Rodriguez, here to talk to you, as I have done at points in the past, about the assessment of persons with cognitive disorders. The point of my presentation today is to try to help sort out some of the various disorders that are not Alzheimer disease. As the title says, we're going to try to call the zebras out of the herd. I'm going to propose a strategy for you to do that, which I hope is reasonably efficient.

In contradistinction to what I've said in the past, I am going to argue today that there are some reasons to try to identify the type of dementia you're dealing with. I want to start with the proposition I put in front of the audience some years ago, which is that identifying the specific type of dementia you're dealing with may not add value. Now having said that, we have to recognize that patients and families typically expect a diagnosis so you have to be concerned for their expectations.

But aside from that, there's a good argument to be made that diagnoses do not help in this situation. And as you can see on the slide, there is no treatment for any of the common dementing disorders. It isn't that we need a diagnosis in order to apply an appropriate treatment.

There really aren't a whole lot of significant differences in the way complications of dementia should be managed depending on diagnosis. Prognosis, yes, it varies a little bit between the various disorders but not a lot. And the range of say life expectancies after diagnosis is so large in most of these that they substantially overlap. You can't make helpful statements about prognosis that are based on specific disorders.

It's also well known by this time, with lots of neuropathology behind us, that people who have dementia, particularly the older patients with dementia, often, almost as a rule, have mixed pathophysiology. So the idea that a single diagnosis would capture the case of that particular patient is often not going to be true.

And finally, in this argument against diagnoses, we're going to make errors. Even the best of us with the best skills and the best set up are still going to make erroneous diagnoses, maybe on the order in optimal settings of even 10% to 15%.

Well having just said that, I'm now going to argue the opposite proposition, that there are some times when you ought to look for a diagnosis. In some cases, a diagnosis does alter management. Some examples would be normal pressure hydrocephalus, where a VP shunt can make a big difference. Lewy body dementia, where antipsychotics can cause havoc and cholinesterase inhibitors may be helpful. Frontotemporal dementia however, is known to respond poorly to cholinesterase inhibitors. In fact, in the behavioral variant, you may promote worsening behaviors with your Aricept.

We want a neurosurgeon involved if we come across an intracranial hematoma or mass. And there would be value in attempting to reduce risk in people with cerebral vascular dementia. And of course, the holy grail in the clinic where we are looking at cognitive disorders is to discover those few remediable cases and fix them. Doesn't happen often but diagnosis can be gratifying, especially if nobody else has figured it out and you're the first. I guess gratifying has to be relative to who we're talking about. In this case, the diagnostician may be pleased to do that.

Another reason that you may want to focus on diagnosis a bit is there are situations, uncommon, where prognosis varies dramatically. These typically have to do with the rare but still possible autoimmune vasculitic dementias, infectious dementias, I list some of those there, and paraneoplastic encephalitis. You may occasionally encounter a patient in whom the diagnosis is going to markedly affect their prognosis.

Families are interested too in diagnoses because the diagnosis may have implications for them. We know about the autosomal dominantly inherited AD. It's rare but those folks are highly likely to develop dementia at very early ages. We talk about APOE epsilon-4, where the risk for developing dementia is 2 to 3 times what it would be in a non APOE 4 carrier in heterozygous and 3 to 5 times greater in homozygotes. Families rightly are interested in that.

You may occasionally see a family where there appears to be clustering of Alzheimer's disease. And in fact, without our being able to quite spell out the mechanism, it's true that risk of developing AD does increase with a number of affected first degree relatives, especially if those first degree relatives develop the disease early in life.

Frontotemporal dementia is heritable on about 30% of cases. And then there are some uncommon heritable dementias. I list one, mostly because its name is so long that it's hard to totally forget.

And finally, reasons for making diagnoses have to do with the possibility that one day, we will see disease-modifying treatment. And when we do, it's going to require us to come up with a specific diagnosis. We may have to take it a step further and specify the stage of that disorder to qualify our patients for that treatment.

If it turns out in some situations to be valuable to make a diagnosis, here I want to propose a way to approach that that really derives from my own experience. Reflecting on what I, in fact, do, I began to realize that I approach diagnosis in cognitive disorders like this. First, I start in with the expectation that what I'm going to encounter is Alzheimer's disease. Typical Alzheimer's disease. In a moment, I'll spell out what that means.

That's not an unreasonable expectations since 60% to 80% of dementia is Alzheimer's disease. I go in thinking that's what I will encounter. As I do my assessment, the history, the exam, and perhaps obtaining imaging, I'm thinking that the evidence I'm collecting does or does not conform to typical Alzheimer's disease. If I'm persuaded that this picture is not fitting with what I had expected I'd see, then I begin to come up with alternative diagnoses, incorporating into my thinking those features of this patient that don't fit with typical Alzheimer's disease.

What do I mean by typical Alzheimer's disease? And this is, by the way, an idiosyncratic definition. I'm not sure you'll quite encounter it in the literature but it fits with a lot of what you will find. First of all, the individual in front of you ought to be over 65 if you're going to conclude they have Alzheimer's disease. There are certainly cases of people much younger but they are unusual.

Secondly, the memory ought to be the concern the patient brings to you. That they or their family are most concerned about, a change in that person's ability to remember what's happening. Memory ought to be prominent. Not exclusive, there may be other kinds of cognitive concerns but memory should be among them and it should be the most prominent of them.

Thirdly, as it's often said, the onset of this problem ought to be insidious. It kind of creeps up on you. And it ought to progress gradually, by which we mean not by sharp increments and slowly. You should not be finding focal neurologic deficits or imaging signs of infarcts, if you're getting CTs or MRIs. There should not be early movement abnormalities, such as the ones I list. Things that look Parkinsonian most typically. And there should not be early psychotic symptoms, delusions or hallucinations.

And finally, in my model of typical AD, there should be no plausible alternative cause of their symptoms. Their review of their medical history and their medications doesn't turn up anything that you suspect could be producing these symptoms. That's typical AD. That's the standard to which we're going to hold the patient. And then we're going to look to see, do they conform to this or do they deviate from it?

The first thing to do is try to drill down on when this problem began. And at that point, what were the signs? In the beginning, what were the first signs? How long ago did they turn up?

When you're doing this, ask about early signs, which may have been dismissed or rationalized. It's often the case that families or other informants don't focus in on developing cognitive deficits until they just can't be avoided anymore. A typical narrative, and I'm sure some of you have already encountered this, is that there was a turning point event. Something happened that finally caused family, friends, co-workers, to realize that, yes, there is a problem. This is not accidental. This is not trivial.

When you get that turning point event, ask, OK, I see what you're saying but looking back at it, were there earlier signs? Were there things happening now, in retrospect, that signal that there was a developing problem? In other words, push hard to establish, as best as possible, the time of onset.

Another trick to use here is to focus your attention on the most demanding tasks that patient engages in on a regular basis. If they're still working, ask about work. Are they performing up to expectations? You'll often get a story there. I've heard this multiple times that there was a change in management or there was a change in the computer system. And that proved to be difficult to accommodate to. I understand that those changes may in fact be difficult but the question that arises is, were others managing to adjust where you could not?

Ask about home repairs. If you've got somebody who's rather handy around the house, those seem to be tasks that are equivalent in a sense to work tasks and may be an early harbinger of problems. For somebody who's a chef, ask about their ability to produce a good Christmas meal. This is not happening in COVID time but say a Christmas meal or Thanksgiving meal with all the dishes in proper order and properly prepared. This is the probe for the time of onset and the earliest signs.

Once you've got that time of onset, move on and try to assess the current status of your patient. This is typically done best with assessing their independence in the activities of daily living. As you all know, there are the instrumental or the complex activities of daily living and there are the basic or self-care type activities. Move through those, asking about which of those that person is no longer capable of performing independently.

Once you've got that information, you can turn to the functional assessment staging test or Tool. It's got various names. It will help you assign a stage to this dementing disorder. Some of you may prefer the global deterioration scale I happen to like it less well but both of those are in common use and they can help you set the stage.

Then make a judgment. OK, I know when this disorder began. I know where it is today. In the intervening time, is it plausible that this could be Alzheimer's disease? Did it progress at a rate congruent with Alzheimer's disease? What I mean by that is that if you are, for example, at stage 4, which would represent mild dementia on the functional assessment scale, it should have been two to three years, at a minimum, that had elapsed from the earliest stages. That, of course, is assuming that you had an informant who is astute enough and observant enough to give you good information on that score.

Here's a case that I ran into, where the rate of progression just did not fit. It's right there in the first bullet. This 77-year-old man who began having memory problems only six months earlier but his Montreal Cognitive Assessment score is 9 over 30. That is just wrong. That is not typical Alzheimer's disease. There's something else going on.

I ask more questions. Well, it turns out, they hadn't wanted to mention it but he began having visual hallucinations about two to three months prior to the onset of memory deficits. Now, it's beginning to look like this disorder, in fact, began maybe nine months ago.

That still didn't fit. He should not be at this advanced stage as judged by the MoCA after nine months. On chart review after the visit, I noted that he had had a large number of ophthalmology and optometry visits with a variety of ill-described complaints. When I say ill-described, I'm not necessarily implying that the patient couldn't describe them but that ophthalmologists and optometrists don't take the most detailed histories. We had a very sketchy sense that he was just bothered by his vision.

They did detect age-related macular degeneration and they treated him with intravitreal injections but his visual complaints just continued to worsen despite that over the course of three years. A year before the visit with me, his wife had taken over the household finances and he had stopped driving, again, because of vision. Now I have a history that suggests well, maybe something was happening for three years and that begins to square better with that MoCA.

Here is his head CT scan. This was red, it is showing diffuse atrophy. If you look a little more carefully at it though, I think most of you would agree that the right posterior area of the brain, the occipital lobe, is markedly atrophic. Look at the size of the lateral ventricle posterior on the right there. That represents the loss of brain volume on that side and the narrowing of the cortex over it also represents that. I'm not confident that I do a better read than radiologists do but I checked in with one of our very expert radiologists for reading scans related to cognitive disorders and he confirmed my sense that, yes, there is occipital atrophy, particularly on the right here.

The diagnosis was posterior cortical atrophy. That's just a description of what that scan shows. But that is a disorder that begins with visual dysfunction and progresses to a global cognitive disorder. The hallmark of it is that these patients seek help for their declining vision through a series of ophthalmologists and it's typically not recognized that this is a kind of cortical visual difficulty not an ophthalmologic. It takes years and sometimes many ophthalmologists before they arrive at that conclusion.

After the visit with me, his wife took him off to see an ophthalmologist, who in fact agreed that no ocular pathology or visual field testing was aberrant enough to explain the degree of his visual dysfunction. They concurred in the idea that this was posterior cortical atrophy. PCA is considered to be a variant form of AD but it also may progress to dementia with Lewy bodies.

Interestingly and sadly enough, six months later, he came in with visual hallucinations that were more complex. And in the interim, he had developed delusions and misidentification syndrome. I decided that he had PCA that was progressing to Lewy body disease. The misidentification was sad. His wife of 50 years was no one to him but a staff member at the facility into which they had moved. And he delusionally believed that he had a new blond wife somewhere. It was a rather wrenching experience for the wife and for the clinician to hear this.

Here's another issue. The first signs, going back to the model I was proposing, that the first signs ought to be related to memory. If not exclusively memory then prominently memory. If you want to be technical about it, it's short term memory, which is interpreted by the neuropsychologist as deficits in delayed recall. You are given a little bit of information, you are then distracted from it for 5 to 10 minutes, and you come back and asked, can you recall this? That's delayed recall. That is the almost paradigmatic type of memory loss seen in early Alzheimer's disease.

You all know the impact of that on daily life. It is fair to say that while memory may be most prominent and the one most troubling to patients, by the time you see them, it is likely that other domains are involved. I list some of those there, roughly in order perhaps of their appearance. OK.

Here's another case where memory was not the initial affected domain. This is 60-year-old man so he already falls outside, just outside, of my model for typical AD. Because he's too young to be developing AD. He came to me complaining about forgetfulness over the past year but it turned out he was still an effective shift manager at a large grocery store. And he was expertly handling the household finances. Not an error. His MoCA score was 30 over 30.

I thought, this isn't really about memory, is it? There's something more going on here. Not to say that his concerns weren't real but what is really pushing this evaluation? Well, it didn't take the family long to tell me that they were much more disturbed by other developments that had occurred over the past two years.

Including an obsessive interest in politics, where he was spending much of his time in social media communicating with fellow believers. His growing lack of interest in or concern for the feelings of family. He seemed indifferent to them. He refused to engage in conversation and would often respond to serious questions from them with little lyrics from songs and lines from movies, which was vastly annoying and upsetting to them.

His wife told me that the only way she could engage him in conversation turned out to be to, in some cases, pretend she had a big purchase in mind because he had developed a new obsessive concern with frugality. He'd become a cheapskate. Those were the changes that really drove the family to ask for this visit, which ostensibly had to do with memory.

I concluded that what I saw in front of me was frontotemporal dementia, the behavioral variant. There are other variants but behavioral is chief among them perhaps. He was seen subsequently at the Alzheimer's Disease Research Center, where again, his performance on testing was quite normal. Maybe a shade less good than it had been the day I saw him. And they too concluded based on a similar history that this was a behavioral variant FTD.

Now, unfortunately for the gratification of the clinicians, the brain SPECT scan did not show hypoperfusion in the frontal lobes as we might have hoped it would if we wanted to confirm our diagnosis. But the ADRC folks remained pretty fixed on the idea that this was just very early behavioral variant FTD.

Another situation where the patient deviates from my expectation that what I'm going to find is Alzheimer's disease. 75-year-old man with a gradually progressive memory loss over one year. But in company with some other developments over that same time frame. He'd become quite apathetic, not really interested in much of anything. And very anergic, not exercising much initiative to get up and do.

When he did get up, he was having difficulty, progressively more difficulty, walking. First requiring a cane and then a walker for balance concerns. He also developed urinary incontinence.

On exam, I found his speech and thought processes to be slowed. His gait was slow and wide-based. And his MoCA took forever to do. I was preparing to abandon it. We finally got through it and he scored 15 out of 30. This is not typical. Alzheimer's disease does not present with those three bullets above.

Here is his head CT scan and I think most of you will be struck by the fact that he has ventriculomegaly. I'll just tell you that in this case, the radiologist felt the ventriculomegaly was congruent with the degree of generalized brain atrophy and the prominent sulci and the narrowing of the gyri.

Now, I didn't do this initially. I accepted their reading and I felt that this was probably unaccountably an advanced form of dementia. At that point, I guess still thinking Alzheimer's disease despite the triad. But there is something known as the Evans index and I put those measurements up there. You measure the width of the frontal horns, that's the top line up there. And then you compare that, you create a ratio to the width of the skull, the inner table of the calvarium in that same slice, that same slice, and you construct a ratio.

Well, the smart doctors at the Cleveland Clinic who saw him because his wife was not happy that we were making no progress, recognized that this Evans index, the ratio of the width of the ventricles to the width of the calvarium, was 0.38, which is well above most people's idea of the threshold for NPH. They tried a high volume lumbar puncture and the results were dramatic. On the drive home, his wife put him on the phone-- The drive home from Cleveland that is. His wife put him on the phone after this removal of some 50 ccs of CSF.

On the phone, I could immediately sense that he was much improved. Dramatic and immediate. He spoke more quickly. His thought processes seemed less retarded than they had. He was just clearly improved. The people at Cleveland Clinic observed that his gait also improved. He went on to have a shunt placed and it had a very major benefit to him in terms of both cognition, his levels of activity, and his gait and balance. What did not improve, and this is often true in NPH, was the urinary incontinence. I suspect that bladder outlet obstruction related to BPH played a large role in that.

Finally, we're leading up to another case here. Is there a good alternative explanation for the findings? I look for those in everybody but I particularly look when I'm uneasy ascribing what I'm seeing to Alzheimer's disease. The places you look are medical illnesses that might cause cognitive change, medication or substance effects, and major psychiatric disorders.

This 72-year-old woman came in with memory problems for two years following a hospitalization where she was confused. At that point, she was given a diagnosis of Alzheimer's disease and donepezil was started. She reported to me, and by the way, she was a pretty excellent historian. She seemed to have well-preserved insight and she was able to describe in some detail what it was she was having difficulty with. It was higher order IADL-type tasks, medications and finances. She stopped driving because she had lost confidence in her ability to do that. Her MoCA was 25 over 30.

There were aspects of this that led me to feel that she deserved a little more close scrutiny. Make sure we're not missing something. She just seemed, in some respects, too good for that MoCA and for the problem she was having. I looked through the records and I found her medications included all of the following. You can see them. I won't read through them all. Interestingly, spironolactone was prescribed for hirsutism. If you have a chance to see those.

And then I considered, which of them might be culprit medications? Topiramate, known as Topamax as a brand, is well known to be associated with cognitive impairment. A neurologist subsequently told me that in neurology circles, they sometimes call it Dopamax. The tremor was also potentially ascribable. Valproic acid, again, cognitive impairment, tremor, increased testosterone, which could lead to hirsutism. She was taking fioricet, which contains a barbiturate, which might also add to cognitive impairment.

I tapered, withdrew, the anticonvulsants and in the process, stopped the spironolactone. Tapered the prednisone, which was for a questionable indication. She actually didn't return. She emailed me, because she lived at a two-hour distance, that she felt her cognition was normal again, that her confidence in her driving had improved, and she felt able to attend Tai chi. She did complain of diarrhea and vivid dreams but those symptoms resolved when the donepezil, which she no longer appeared to need, was stopped. I think this is that extraordinarily rare zebra where you do find somebody, who, at this point, actually has the label of Alzheimer's disease but turns out to be suffering adverse medication effects, a remediable cause.

I should add here that among the tools we might use to help clarify what we're dealing with is neuropsychological testing. A neuropsychologist can often tell you that the pattern of deficits seen on testing conform to the diagnosis that you are suspecting or don't. That can be of value.

Here are some more tools for improving diagnostic accuracy. Because I think we're going to be expected to do that. If we're not already expected, in terms of what patients and families bring to the encounters, we're going to be expected when and if there are treatments available. These are things we've got already.

Structural MRI, which can show you atrophy that is congruent with the diagnosis you're suspecting or not. SPECT scans, Single-Photon Emission CT, can show you regional hypoperfusion in the areas that you might expect to be affected and that may precede the presence of atrophy on MRI. In other words, the functional deficits begin to occur before the structural or anatomic. Same thing goes for FDG PET, which looks at regional metabolism.

Here are other tools. Now, these are not in general clinical use yet. They are certainly being used in research settings but they may become available. I have a sense that the insurers will throw up barriers until we need them in order to direct people appropriately to treatment or not. CSF assays. Beta amyloid 42/40 drops in the CSF as the disease progresses. The idea being that more of it is being deposited in the brain and therefore not making its way to the CSF. Phosphorylated tau however, a marker of neurodegeneration, increases with progression of the disorder.

PET imaging with these radioligands for abnormal amyloid and tau. We have amyloid scanning with florbetapir. A negative scan means that the likelihood of Alzheimer's disease is pretty low. Not impossible but unlikely. A positive scan certainly raises the likelihood that you're dealing with Alzheimer's disease but it may be seen in normal controls and in persons with other causes of dementia. It's not perfect in that respect.

Tau scanning with flortaucipir looks pretty promising. It may correspond better than the amyloid scan to the areas of expected atrophy. It may also correspond to the clinical stage and the rate of progression. Tau scanning, which has come along after beta amyloid scanning, looks quite promising.

Then there's the new big thing, which is enough to make me think that if you had some spare change, you would look for the companies developing these, maybe make an investment. These are the plasma protein assays for screening and confirming diagnoses. There's a beta amyloid protein assay so you can test blood for the presence of beta amyloid. It is being marketed as PrecivityAD. I'm not sure that insurers will pay for it but it is available. I've not used it.

And not yet at that stage to my knowledge are plasma levels of phosphorylated tau. And tau comes in a whole bunch of isoforms. The one that seems to be attracting the most attention is that 217. It is performing rather remarkably in terms of its ability to confirm diagnoses and differentiate Alzheimer's disease from other dementing disorders. Then there's a more obscure plasma assay, neurofilament light.

The advantages of these plasma assays are pretty evident, as opposed to PET imaging and CSF assays. First, they're looking to be much cheaper than PET and I give an example of the difference between Precivity and a PET scan. They are more scalable because doing PET scanning means that, probably, you have to have an on-site cyclotron to produce the radioligand and then you've got to have the PET scanner. That is not going to be happening at most hospitals.

They are clearly less invasive. It's a blood test not a lumbar puncture. And the plasma tau looks more sensitive than the PET tau imaging in early or preclinical disease. Look for those.

Finally, I just want to say that having presented this strategy for making diagnoses, I want to point out some pitfalls to be honest about it. First of all, there's a lot of atypical AD out there. It's the minority of AD but it is there. It includes the primary cortical atrophy that I talked about in the occipital areas. Then there's primary progressive aphasia, which is also considered to be a type of Alzheimer's disease in that it is based on amyloid and tau deposition. And finally, at least for now finally, there is a behavioral or dysexecutive variant of frontal affecting AD.

There are also, as I alluded to earlier, many people with mixed pathophysiology. The common combinations would include AD with cerebrovascular disease or with Lewy body. And recently, there has been described this type of dementia known as LATE. You can read the full name of it there. Which presents, clinically, very similarly to AD.

There are some curveballs in the midst of this attempt to simplify and make more operational the evaluation as I've been trying to do here today. I think the big new thing is coming in terms of diagnostic testing and perhaps, one day, the treatment to go along with that diagnostic testing.

In my final slide, I'm just going to let you know that we are likely to be back with more and hopefully some good news. Thanks to Arnold there. That's all I've got for today. Thank you.