By David S. Geldmacher, MD

Whatever Happened to Pick's Disease?

The fate of this outdated diagnosis exemplifies the shortcomings inherent in the classification schemes for dementia.

Not long ago, I was speaking to a small group of neurologists on differential diagnosis of dementia. At the end of the lecture, a clearly respected senior member of the audience posed a question. His inquiry, preceded by a lengthy commentary reflecting his expert training in neuropathology and extensive experience with dementia diagnosis "way back when," was essentially, "How could you have left out Pick's disease?" Since the lecture had included a careful review of the diagnostic criteria for fronto-temporal dementia, and a discussion about the illness's variable clinical expression, I was a bit surprised.

Now, I admit that I can rarely sustain consciousness for an hour when I attend a medical lecture, so I wouldn't have been surprised if he had nodded off for that section of my talk. However, the intimate small-group setting allowed me to be pretty sure he'd been awake and attentive the whole time. It was then that I realized the nature of the problem: someone had gone and changed the name of Pick's disease and he'd missed the pronouncement.

I recognize now that I shouldn't have been surprised. The nosology of this illness is notably complicated, and has been eloquently summarized by Andrew Kertesz from the University of Western Ontario.[1] In 1892, Arnold Pick described the typical features of the disease, including aphasia and prominent behavioral changes, and noted their relationship to frontal atrophy. Subsequently Alzheimer identified argyrophilic inclusions (Pick bodies) in association with the symptoms and, along with ballooned cells, neuronal depletion and gliosis, these became the defining features of "Pick's disease." There was a problem, though. You see, not everyone who had clinical Pick's disease had Pick bodies on neuropathologic examination, and not everyone with Pick bodies had clinical Pick's disease. It was clearly a situation ripe for change.

What's in a Name?

The problem was that not everyone agreed on how the condition should be named. A panoply of alternatives therefore emerged, with frontotemporal dementia or FTD being the most commonly recommended alternative in the last few years.[2,3] More recently, the ongoing taxonomic struggle between *lumpers* and *splitters* has edged toward the splitters, with many clinicians adopting a three-way division of the disease state into a frontal variant, semantic dementia and primary progressive aphasia (PPA, sometimes also known as progressive nonfluent aphasia).[4] At the same time, the biochemical and molecular biological descriptions of these diseases as converged on abnormalities of the cytoskeletal protein tau, and the gene that encodes it on chromosome 17. Tau is, in fact, a primary component of the Pick body (but also the neurofibrillary tangle in AD). The so-called tauopathies cover an even broader clinical spectrum than FTD, including progressive supranuclear palsy, corticobasal degeneration and amyotrophic lateral sclerosis, but not AD. Still, not all cases of FTD are associated with tau mutations or pathological accumulation of tau.

It is abundantly clear, at least with current knowledge, that no one classification scheme captures the complex clinical, pathological, biochemical and molecular biological variations in individuals with the FTD pattern. That makes communicating clearly with colleagues and patients very difficult. Kertesz aptly summarized this challenge when he wrote, "Try to explain to the referring general practitioner or to the family, who were told the patient had a variety of Pick's disease with primary progressive aphasia, why the pathologist's report says corticobasal degeneration (CBD)!"[1]

I can understand my audience-member's yearning for simpler times in dementia diagnosis. What once appeared to be a set of simple dichotomies has now gotten very complicated. When I was first learning this field, dementias were often classified as senile or presenile, and cortical or subcortical in expression. If the patient's findings were cortical and presenile, then the dichotomy was Alzheimer's vs. Pick's. If behavior was worse than cognition it was Pick's; unless, of course, it was syphilis, but you could test for syphilis.

One by one, those dichotomies have been struck down. It was the 1984 NINCDS-ADRDA criteria that eliminated the "presenile" from the expectations of AD when they stated that AD could have its onset between the ages of 40 and 90. The cortical/subcortical dichotomy has always been problematic, especially when we reflect that there is far more neuronal loss evident in the deep nuclei of the AD brain than there is in the cortex. The Alzheimer's criteria allow for prominent language dysfunction, but now both fluent and nonfluent types of progressive aphasia are often classified with the FTDs. How do we make sense of all of this confusion?

There is an alternative way of thinking about the problem that has strong appeal in clinical settings.[5] Instead of trying to impose syndromic distinctions on what appears to be a multidimensional continuum of genetic and biochemical contributors, we can take a behavioral neurologist's approach. We can think about clinical patterns that suggest right vs. left and tempo-

ral vs. frontal dichotomies, but we need not consider them as mutually exclusive. Thus, an individual might have dysfluent aphasia early in the disease process, reflecting left frontal dysfunction. Later the dysfunction might spread to reflect a more bifrontal and left temporal pattern, expressing apathetic behavioral changes and increased problems with language comprehension.

Acknowledging my biases as a nonsystematic observer, I think this is what I see happening with many of my FTD patients. A much more systematic follow-up, including autopsy, was reported by Kertesz and colleagues, who showed that most patients initially presenting with a PPA or FTD pattern would eventually develop the other syndrome, or a related illness like corticobasal degeneration or motor neuron disease.[6] Other authors have reported that many clinically diagnosed cases of PPA turn out to have AD pathology at autopsy.[4]

Linking Pathology with Behavior

Translating this localization-oriented approach to clinical practice can be difficult, especially when trying to explain the subtleties to patients and family members who may have been expecting to hear an Alzheimer's diagnosis. Many FTD patients are referred to me for second opinions having been told they have AD, but I see relatively few referrals that specifically identify FTD. However, I find a systematic neuroanatomic approach can help me sort these cases out. I think differentiating these disease states is important, because it helps to clarify the pathological basis of the behavioral and cognitive abnormalities, identify appropriate therapies, and better predict the course.

I start by thinking about what is most disabling to the patient and family. If behavior and comportment are worse than memory, the pattern points toward a right frontal or bifrontal-predominant FTD. Many, but not all, AD patients will have complete preservation of social skills in mild dementia, but FTD patients often seem, or are reported to act, odd. Poor memory for recent events is almost always the leading problem in AD, but the memory problems reported to me in FTD are often associated with forgetting how to behave rather than forgetting things they have done.

The behavioral abnormalities of FTD need not be the disinhibited, inappropriately jocular changes which localize to orbitofrontal dysfunction. In my practice, signs associated with mesial and dorsolateral frontal dysfunction like apathy, emotional blunting and perseveration appear more commonly. These often get treated as depression, even though the patients deny any low mood or blue feelings. Failure of SSRIs to relieve the symptoms can give us a hint that the problem might be frontal apathy rather than true depression.

FTD with a left frontal predominance will demonstrate a progressive nonfluent aphasia, often accompanied by reduced verbal output. In contrast, the left temporal pattern, or semantic dementia, can be characterized by loss of word meanings. One of my patients with presumed semantic dementia once said, *"I hear the word supermarket, and I know I used to know what that meant, but now I just don't know what 'supermarket' means."* These language problems can often be differentiated from the linguistic dysfunction in AD, in which naming difficulties are most prominent. The AD patient's speech may *seem* dysfluent, but the effortfulness evident in their speech often reflects word-finding difficulties. AD-type word-finding problems show up on naming tests where patients may say, "I know what it is, but I can't remember what they call it." The left temporal lobe dysfunction patient often doesn't "know" the name of what the drawing represents and may seem confused by the task.

Imaging is another way of differentiating AD from FTD. In AD the hippocampal region is specifically atrophic, but in FTD broader regions of the frontal and temporal lobes are affected. Many radiologists are not cued in to these subtle differences, so it might require personal review of the images or a call to the radiologist to clarify exactly how any temporal lobe atrophy is distributed. These days, we also have PET scanning—Medicare approved for the AD-FTD distinction—but prior approval requirements and tight restrictions set by private insurers often make obtaining a PET scan a clinician's nightmare. (See *Practical Neurology*, Oct. 2005, Vol. 4, No. 10 for more on this topic, available online at www.avondalemedical.com/ PN_archive .htm.)

Gone But Not Forgotten

So, the question of "Whatever happened to Pick's disease?" is, in fact, a good one. Right now, the answer is that it disappeared under a sea of confusing information and conflicting evidence. In that process, it has undergone permutations in nomenclature, contributed to the discovery of a multitude of unsuspected relationships among neurodegenerative diseases, and remains one of most challenging clinical conditions for us to manage. Maybe it was simpler when there was just Pick's disease and Alzheimer's disease among the presenile dementias. Nonetheless, I'm sure that all the confusion these days means we're much closer to effective therapies for these folks than we were "way back when." **PN**

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