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Case Report

It's the Brain, Not the Eyes

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Abstract

Purpose: To discuss posterior cortical atrophy, a rare neurodegenerative dementia that begins in midlife and marked by visual and spatial changes that can be mistaken for cataracts and other ophthalmic disorders.

Participant: A man in his 60s who was eventually diagnosed with posterior cortical atrophy and began having visual and spatial symptoms that progressed to include behavioral changes.

The Science: Descriptions of the science and the case study offers the opportunity to identify potential patients during a routine ophthalmic exam.

Conclusion: Ophthalmologists will learn about the progression of this midlife dementia.

Keywords: *Posterior Cortical Atrophy; Visual and Spatial Dementia; Atypical Dementia; Ophthalmology*

Introduction

Posterior Cortical Atrophy (PCA) is a visual and spatial dementia that begins in the occipital and parietal lobes of the brain and slowly spreads to other regions. Over time, they become cortically blind. Their eyes are not the problem. It is the information that is taken into the eyes and delivered to the brain's visual system that is building up pathology. It is often the same pathology found in the brains of Alzheimer's patients - the amyloid plaque and tau tangles - but it starts accumulating in the areas of the brain that regulate vision and spatial processes and triggers symptoms in the prime of midlife. Ophthalmologists could be the first line of defense if they understand the condition before turning to the more obvious visual problems caused by cataracts and other eye disorders.

The symptoms

Visual disturbances in PCA remain the primary feature, and some patients show a relative sparing of memory far into their disease progression. Patients have difficulty locating objects in plain sight; judging spatial relationships; navigating; recognizing visually presented objects and faces; understanding written words or having trouble writing and calculating numbers. These people are learning to navigate a world in which they don't see enough of the whole picture to make sense of what it is. Their world is seen in slivers of light and form and they no longer are able to make out objects right in front of their eyes.

Case Report and Discussion

In 2009, Steve could stand up at a meeting and people would listen raptly to what he had to say. On the way home, he would sit comfortably in his 1955 DeSoto and grin and wave to people in other cars. Then, people started honking when he passed, and it wasn't because they were excited to see his vintage car. This happened with increased regularity. He'd scream back. He began noticing that he'd get to a turn in the road and press his foot down hard on the brake because he didn't know which way to go. A short time later, the landlord complained that it looked as if a three-year-old had filled out the rent check. None of the information was in the right place. His name was scrawled at the top of the check. It was scary.

Steve was soon told not to come back to work. He got a new job but lost it on the first day when he could not complete the paperwork. Getting lost was as commonplace as getting up in the morning. He could no longer write on a straight line. In fact, he couldn't even see the line.

His wife, Kay, also knew something was wrong. They were driving across Lake Shasta. He insisted he could drive. He was in the fast lane, and he was going way too slow. His hands were tight on the wheel. His knuckles were white. Kay is generally calm, but she was now in panic mode. She guided him into the right-hand lane, gently holding the steering wheel. They pulled over when they got over the bridge. And that was the day she took control of the wheel - and just about everything else in her sweet husband's life.

"There is something wrong in my brain", he had said a few months earlier, in the middle of a presentation at work. He had begun sobbing. His colleagues just stared. For the next decade, this would be Steve's refrain: "My brain is broken". At first, he would cradle his head in his hands, rocking it from side to side. In the months preceding his death, which was in late October 2020, he would pound his head on a wall or a door. He knew that something was wrong with his brain. He wanted out of his body.

In 2011, two years after the first obvious signs that there was something serious going on, Steve was diagnosed with PCA. For the majority of patients, this visual/spatial dementia most often involve the same toxic proteins - beta-amyloid and phosphorylated tau - that build up in the brains of people with Alzheimer's. But the difference is that these proteins accumulate in the brain's occipital lobes that oversee how we perceive the world, and the parietal lobes just north of the occipital lobes that integrate sensory input.

There are other toxic proteins that can cause PCA. No one is sure why the toxic proteins are accumulating, and why it starts a decade or two before people develop the first clinical signs of Alzheimer's.

Right after the trip to Lake Shasta, Kay took Steve to an optometrist, who ended the examination saying that he had a left visual field defect. A slice of the world was no longer visible to him. They thought it might explain why he couldn't see lines. Why his writing was mere scribble. Why he was getting lost.

But things were getting worse, and they went to a neurologist who ordered the works: a spinal tap, an MRI, a PET scan, blood draws, and a few hours of cognitive testing. In the end, the neurologist said: "I don't know what it is. It looks like Alzheimer's but not quite". She referred him to the UCSF Memory and Aging Center, dubbed the MAC, where I was an Atlantic Fellow for Equity in Brain Health. Steve was sixty-one.

A neurologist at the Memory and Aging Center didn't think he needed the MRI results to know what was wrong with Steve. But testing was repeated and Steve was officially diagnosed PCA.

UCSF's Gil Rabinovici became Steve's neurologist. Dr. Rabinovici took to PCA early in his career. By the time people arrived in his examination room, they had been through a maze of misdiagnoses: Ophthalmologists took them in for cataract surgery; psychiatrists said it was all in their heads. Even neurologists often got it wrong and diagnosed them with an early stage of Alzheimer's, encephalitis, or stroke.

"It takes a good ophthalmologist to figure out that this is a brain problem", Dr. Rabinovici said. "Then, it takes a good neurologist to figure out that this is a neurodegenerative disease". In 2017, he and other PCA experts created the first international guidelines for the neurological condition.

I met Steve and Kay the year the PCA guidelines were published. It was six years after his official diagnosis, and he was still partaking in many of the activities that came to define his life. He had been a triathlete and a long-distance runner, and he was still biking and running, although he was having trouble judging the terrain. He could still do 120 sit-ups a day. His heart was filled with love for his wife. During one of our visits, he teased her and said that he was her "stud muffin". His eyes twinkled.

By then he could no longer write or easily read words on a page. Kay dressed him in ways big and small: selecting his daily outfits and then putting on his clothes and shoes and buttoning his shirts. She accompanied him into restrooms. He didn't recognize objects or remember what they were for. He bumped into furniture. He shuffled to balance himself. He was also uncharacteristically quiet, withdrawn, disengaged. Kay said that it was hard for him to find words to talk about the subjects he had always loved: astronomy, planets, global warming, and politics. He was not aware of all the things he could no longer do.

He was never a picky eater, but by the time I met him the menu boiled down to pot pies, peanut butter and jelly, oatmeal, and egg sandwiches. Friends would come and take him running, but he would constantly veer off the trail.

In January 2018, Steve wanted to attend the March for Women rally in San Francisco, and Kay agreed to take him. As was usual at that point, she held his hand to guide him. But he missed a curb and fell, taking Kay with him. She had already undergone surgery after breaking her left arm, and the impact jammed the titanium plate in her upper arm into her collarbone. The damage was severe enough to require shoulder replacement.

Her new surgery was scheduled, and she had to find temporary housing in a memory care facility for Steve because she could no longer care for him: dress him, brush his teeth, help him get through his night terrors. She found a facility, which required a five-thousand-dollar community fee and the first month's payment.

At first, Steve danced and engaged with the staff, but progressively he became confused and disoriented. He was the problem child of the facility. He was often angry. Seven months later, in January 2019, he was lost in his rage. Kay believed that he was acting out because he felt betrayed and abandoned by her, the one who had put him there. But it was the disease.

The director finally called the police claiming a "5150", the number of the section of California's Welfare and Institutions Code that allows a person with a mental challenge to be involuntarily detained for a seventy-two-hour psychiatric evaluation. The EMTs who responded were able to talk to him and get him to agree to go to a local hospital's emergency department for an evaluation, meaning that he would not be taken in on a 5150. It was a narrow escape.

The emergency room physician was unprepared for a patient in Steve's condition and wanted to send him home. Kay refused, saying that she felt he was a danger to himself. Arrangements were made for him to be on hospice at home until he could be admitted to a different facility. She did find a new place, with another hefty community fee.

In July, he got out of bed at the new facility in the middle of the night, looking for help finding the bathroom. He walked around for hours, screaming. There was no staff around to try to stop or calm him. Finally, a frail man on hospice lifted himself out of bed and opened his door to see if he could get the yelling to stop. Steve pushed him, and the man fell and broke his leg. He died three days later. Steve was evicted from the facility.

Kay found a dedicated memory care facility, this time with a roommate. And a third community fee. Kay brought a spin-bike into his room, thinking maybe he could ride out his frustrations.

There were still moments of wedded bliss between Steve and Kay. But in this new memory care facility he began having hallucinations, seeing people who were not there. On September 28, 2019, the two of them danced at a party at the facility. By then, he would say casually that she needed to find another man. "But you are my man. You are all I can handle", she told him.

On October 1, the facility administrator called and said that Steve had torn his bed apart and that he had the sheet wrapped around his neck. They were able to distract him, but five days later, he could not be distracted. He was pacing and shouting. "This isn't real!" he cried. He began hitting his head on doors and walls. He cried out: "My brain is broken. My brain is broken!".

When Kay arrived, he asked her: "Are you real?" She was able to redirect him for a moment, assuring him that although she didn't know everything that was real, she knew their love was real. He was able to remain calm for another twelve hours.

On October 10, the left side of Steve's body became paralyzed. He was transferred to the emergency room. He was out of control and flailing, fighting to get off the gurney. Wanting to calm him down without restraints, the emergency room staff moved him onto a bed that raised his knees and lowered his head just a bit. It worked to immobilize and calm him. Within days they moved him into a hospice bed.

Steve thought that Obama was still president, and that the president wanted him on his team. Friends and family visited. His very last words were spoken to a caregiver: "I have the best wife ever. She loves me". He died ten days later, on the last Friday of October.

One of the first calls his wife made was to the UCSF Memory and Aging Center. Eight years earlier he had signed an authorization form to donate his brain to science. Steve's brain arrived at UCSF within hours of his death and was immediately sliced and divided into sections. Half was fixed in formalin and the other half was frozen for research.

At death, his brain tissue had shrunk considerably. The naked eye could see the damage. The pathologists spent more than six hours cutting sections of the brain into one-centimeter-thick slices. Not surprisingly, there was severe atrophy in the back of the brain, which explained his visual and spatial problems. There was cortical thinning and moderate hippocampal atrophy, and severe neurofibrillary tangle pathology in many areas of the brain - beginning in the back but having spread by the end to the front of the brain.

An autopsy allowed pathologists to identify the location of the pathology and the extent of the damage, and then they tied it in with the brain scans, clinical evaluations, and the team's diagnostic suspicions that were made a decade ago. Ten months later, a final diagnosis was made by neuropathologists Lea Grinberg and Eric Huang. The primary pathological diagnosis was Alzheimer's, with the classic amyloid and tau pathology and shrinking of many brain regions.

Steve had a sharp memory until the end, although his emotional and behavioral circuits were on fire. PCA can also reflect a mix of other pathologies, and the reason that an autopsy is so important is that it provides clues about the disease. Steve's earliest visual and spatial symptoms may have actually started when he was in his fifties. So, he had the clinical syndrome of PCA, but the pathological diagnosis at death was Alzheimer's. (This makes sense, since most PCA patients have amyloid and tau pathology seen in Alzheimer's, but it begins in the visual and spatial centers of the brain and spreads from there).

Identifying and defining PCA

Back in the late 1980s, neurologist D. Frank Benson, one of the pioneers in the field of behavioral neurology, published a study on a series of patients with deficits in higher visual function and sensory aphasia. The UCLA scientist and his colleagues were managing a

handful of patients who could not see things that were right in front of them. They couldn't keep hold of numbers or know what to do with them. In time, they became cortically blind. Their eyes were still functioning but the information coming in through them was not being processed correctly once it arrived into the visual cortex.

Dr. Benson was an astute and compassionate neurologist. Without any pathological clues, Dr. Benson thought it was an atypical clinical variant of Alzheimer's. He coined the term posterior cortical atrophy. It was definitely a puzzle, because on autopsy Dr. Benson went on to find that the pathology of Alzheimer's was showing up in the wrong place. It was in the occipital and parietal lobes.

He published his small case series of five patients with problems in higher visual and sensory processing, Around the same time, there were already other rare atypical dementias - language dementias and behavioral dementias - being identified and studied [1].

In 2017, three decades after Dr. Benson's discovery, behavioral scientists finally created a common language to talk about PCA. Heading the effort to create this diagnostic roadmap were UCSF's Dr. Rabinovici and neuropsychologist Sebastian Crutch, an Alzheimer's senior research fellow at University College London (UCL). While a few centers had independently published diagnostic criteria, including UCLA, there was no universal agreement on how best to identify the most salient features of PCA and arrive at a more uniform diagnosis.

Few neurologists had ever seen a person with PCA, and many didn't even know it existed. Optometrists and ophthalmologists were generally first in line, and they were focusing not on the brain but rather on the eyes. People would undergo cataract surgery and go for years without knowing that it was their brain and not their eyes that were not working right.

Five years earlier, in 2012, Drs. Crutch and Rabinovici and a long list of collaborators published a review paper in the scientific journal Lancet Neurology highlighting problems with the criteria at the time. They brought together an international group of doctors and scientists to create a unified diagnostic language. They were particularly interested in the impact the diagnosis, or misdiagnosis, would have on research.

For instance, people with PCA were often not considered in research studies that were heavily weighted to identify changes in memory. These patients, at least in early stages, don't have memory problems. When scientists were considering adding PCA patients into their clinical trials there was a question about whether the tests being used to measure outcomes, which were mostly designed to test memory and cognition, would even be meaningful. People with PCA have a hard time processing visual information, but they could soar through the memory tests, so it would be problematic to compare outcomes in treatment trials.

There were many other reasons for a consensus on diagnosing PCA. For one thing, data from individual groups may not represent what is happening in clinics around the world. The condition is thought to be rare. By 2017, the UCLA group had seen only about 120 people who met the criteria for a diagnosis at their center, the UCSF group about a hundred.

The clinical signs vary from person to person. We come to these diseases with a lifetime of who we are, and that often factors into the events that play out under the burden of toxic brain proteins. The primary features that they were seeing included a wide range of vision changes and deficits in calculating numbers and writing. Some people, like Steve, had greater problems seeing and making sense of spatial relationships - where things are - and other people had more trouble with object perception - what things are. Most people couldn't see visual details and complained of problems calculating or planning movements. Others had field cut difficulties with lights and color and elemental aspects of visual perception. Many had difficulty reading and writing.

Location is everything in diagnosing neurodegenerative brain diseases. Neurologists generally use the most prominent first symptoms and make their best guess as to what pathology is driving the condition, and where in the brain it begins. Scientists say that about 90

percent of people with Alzheimer's will have visual problems later in the disease process, so it is important that neurologists take a detailed history of the earliest signs. Most patients whom the PCA consensus guidelines described had a similar pathology to add, the amyloid plaques and tau tangles, but in a different location. Yet there were definitely people with other neurodegenerative conditions, such as Lewy body dementia, corticobasal degeneration, and prion disease, who also had visual and spatial problems. These conditions have their own abnormal proteins mucking up neurons and other cells in the brain.

Conclusion

There is growing evidence in neurodegenerative diseases that abnormal proteins replicate and spread like a slow fire. In the case of PCA, it may begin in the occipital and parietal lobes, but over time the diseased cells begin showing up in other regions, and people can have cognitive problems, and memory and/or behavioral issues. The evidence is there: When neurologists look at scans late in the disease in people with PCA, or pathologists look inside the brain at death, there can also be damage in the frontal and temporal parts of the brain.

Many people ask whether PCA is genetic, and at this point no one really knows. Scientists are looking. In one study, Jonathan Schott, a neurologist at University College London, and the international PCA working group collected DNA from three hundred patients and found two genetic markers that could be risk factors for PCA. One is involved in the development of the visual cortex and another with cholesterol. The most common risk gene variant for late-onset Alzheimer's - apolipoprotein e4 - also appeared to be a modest risk factor, but it wasn't as strong as it is for people who go on to develop the more typical amnestic form of Alzheimer's.

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Conflict of Interests

There are no conflicts of interest. This case study was excerpted and modified from a book on atypical dementias written by the author and published in January 2023.

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