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A Case of Semantic Variant Primary Progressive Aphasia with Severe Insular Atrophy

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Abstract

Insular degeneration has been linked to symptoms of frontotemporal dementia (FTD). Presented in this case is a patient exhibiting semantic variant primary progressive aphasia, behavioral disturbance. Upon autopsy, he was found to have severe insular atrophy. In addition, selective serotonin reuptake inhibitors (SSRIs) were ineffective in reducing symptoms of obsessive-compulsive behaviours or emotional blunting. This case suggests that Seeley et al.'s hypothesis that VEN and fork cell-rich brain regions, particularly in the insula, are targeted in additional subtypes of FTD beyond the behavioral variant.

Keywords

frontotemporal dementia; MRI; PET; SPECT; insula

Introduction

Frontotemporal dementia (FTD) is a neurodegenerative illness in which the insula may be preferentially affected. Seeley et al. have described the exquisite vulnerability of von Economo neurons (VEN) present in the insula and anterior cingulate cortex (ACC) to neuropathologic changes of frontotemporal lobar degeneration.¹

Electrical stimulation during neurosurgery first indicated a role for the insula as a modulator of visceral emotional responses.² Functional MRI and PET studies within the last 10 years have more recently linked insular activation to the perception of emotional expressions, as well as to the generation of emotion within an individual.³ There is a relationship between insular atrophy and symptoms of behavioural FTD. For example, atrophy in the right ventral insula is associated with compulsive binge eating, despite normal taste recognition in FTD patients.^{4, 5}

We describe the clinical and autopsy findings in a patient who was followed closely in a Behavioural Neurology clinic for semantic variant primary progressive aphasia (sv-PPA) and marked behavioural disturbances that began relatively early in the course of illness. Medical management was difficult because of his notable intolerance of the usual serotonergic and antipsychotic agents prescribed to patients with symptoms of FTD.

Case Description

A 58 year old right handed man with 14 years of education presented to the UCLA Behavioural Neurology Clinic with a chief complaint of memory loss. He had worked as a salesman and then owned a lamp manufacturing company for 38 years before retiring. The patient had been having trouble remembering names for the last 3 years. He had also developed difficulty with language comprehension, curtailed his reading, could not concentrate, and was noted to be much more facetious by his family.

Initial Examination

On mental status testing at presentation 3 years into his illness, the patient's behaviour was appropriate to the context of the visit. His verbal output was fluent, but with a distinct emptiness. He circumlocuted, attempting to give descriptions for nouns that he was unable to produce. His comprehension was intact for simple commands, as demonstrated by pointing accurately at objects about the room or answering yes/no questions appropriately. His repetition was very well intact. On the Boston Naming Test (BNT), he was able to name only a few of the most commonly-used words (tree, bed). Although by history he was not reading as much for pleasure, he was able to read sentences aloud without difficulty. In formal neuropsychological evaluation, there was a striking discrepancy between verbal (VIQ= 77) and performance (PIQ= 110), with impairment isolated to language function. Semantically significant words had lost their symbolic meaning. In contrast, the patient was able to handle syntactical language in a basically normal manner.

He showed no impairment on tests of attention or mental control in year 3 but was unable to determine similarities and differences, or to interpret idioms or proverbs, almost completely because of his aphasia. When asked "How are an apple and a pear alike?" he responded, "Pear, Pear, I don't know what a Pear is," which may be described as word alienation. One year later, word alienation had progressed, but the patient was still able to repeat simple sentences. On the Frontal Assessment Battery at 3 years into illness, the patient performed well on reciprocal programs and go-no go. He was able to perform the Luria hand sequences without errors. He showed no evidence of ideomotor apraxia.

Memory was tested with an 8-item supraspan word list: his learning curve over 4 trials was 2, 3, 4, 5; after 15 minutes he recalled 4 of the 8 words spontaneously, not benefitting from category clues and retrieved only one additional word from multiple choice. He had similar impairment in non-verbal recall. He showed good memory for current events and presented his own history with little correction or prompting from family members; thus he appeared to have good insight at presentation.

At 3 years, visuoconstructive function for figure copy was intact. When asked to generate a drawing on command, however, he was able to make a circle but was unable to place the rest of the features of a clock. He had no difficulty with right/left discrimination or finger gnosis. The impression at this time was that of a primary progressive aphasia, specifically semantic dementia.

Disease Progression

At 5 years, the patient could only score 3/15 on the abbreviated BNT. In year 9, the patient was still able to mimic one step commands. Folstein Mini-Mental State exam scores declined from 27/30 to 24 at 5 years, 21 and then 14 at 7 years. The fact that the patient's figure copy was still intact on the MMSE at year 9 supported a diagnosis of FTD more than Alzheimer's disease. He was, unfortunately, unable to complete the rest of the MMSE due to his advancing aphasia.

By year 10, the patient was variably able to copy a complex figure. At year 13, he was unable to recognize pictures of familiar people. Full testing was not possible, but he had significant difficulty with language, both reduction of output to verbal stereotypies and palilalia, as well as in comprehension.

Behavioral Disturbances

Four years into illness, his Neuropsychiatric Inventory (NPI) score was 4/144, with mild scores for apathy and disinhibition simultaneously. The following year, behavioral changes became more prominent than the aphasia. The patient was more talkative and disinhibited with strangers. Behavioral changes noted for year 7 included an increase in inappropriate laughter, decreased libido, a rigid time-table for meals, and routinized or stereotypic eating behaviours, such as counting all the pepperoni pieces on the pizza before he could eat. He would count everything. The patient apparently suffered a traumatic incident while washing or being washed and subsequently developed hydrophobia, fearful of the shower and rain, which persisted throughout the remainder of his illness. In year 9, the patient was having verbally agitated episodes in the bathroom. He would berate himself, but these were short-lived episodes.

The following year found the patient occupying himself at home with computer games and puzzles during the day. At year 11, he had angry outbursts, was inappropriately loud in public, and was increasingly familiar with strangers, wandering out into the street several times per day after disarming the home alarm system and pacing when indoors. A new compulsion was nose-blowing, up to 75 times daily, and he had a new verbal stereotypy, "I'm Alzheimer's." A new routine was waiting for the delivery of the morning paper. He began to use the floor of the bathroom as opposed to the toilet. On examination he was awake and alert, was much less outgoing and euphoric than on previous visits, and made poor eye contact. He had blunted affect and could not understand any commands. When not blunted in affect, he would be sad and tearful with self-deprecating statements.

By year 12, the verbal stereotypy was reduced to responding "no" to every question or comment and addressing familiar women in his household as "honey". There was some evidence of palilalia. He had become fully dependent for basic activities of daily living but on a rigid routine. The patient maintained his interest in playing board games, happy to be among people most of the time. For example, after being separated from his wife for the examination he returned to her room to make sure she was still there and stated "you are here, and that is good". At other times, the patient showed excitement over seeing his daughters after long intervals. Contradictory to these signs of affection, there was emotional blunting, in that if his wife was ill, he showed no clear understanding or concern. Another example of his retained social graces was a sense of modesty in the bathroom with his female caregiver. He would not allow her to help him with hygiene, although he would also have incontinence in public without concern, often smearing his feces over surfaces if left unchecked.

At year 13, the patient began to eat to excess, with an emphasis on bread, cereals and pasta. This led to a 40-pound weight gain.

Neurological Examination revealed stable anisocoria, bilateral resting tremor after the first 10 years of illness, inconsistent hyperflexia and no frontal release signs.⁶

Medication trials: donepezil 10 mg daily at 6 years equivocally caused a complaint of diffuse joint pain in left elbow, migrating up to both shoulders and down to the wrist, additionally in the left knee. The myalgia may not have been related to the cholinesterase inhibitor use, because the patient continued to have symptoms even after he stopped taking the medication. At 7 years, the patient was tried on clomipramine 25 mg orally per day for obsessive-compulsive behaviors, but this resulted in hyperhidrosis when dosage was increased from 25mg daily to 100 mg. Paroxetine caused stomach aches and hyperhidrosis at doses of 5 and 10 mg per day. Sertraline 50 mg, the 3rd drug for compulsions, was also not well-tolerated, for reasons unavailable from the chart or family members. Valproic acid was not noted to cause adverse effects. Quetiapine 25 mg daily resulted in more calmness and better sleep habits in year 9. Citalopram up to 10mg po qAM to 10 mg po BID, then escitalopram 10 mg daily, haloperidol 1 mg daily, then olanzapine 15 mg po daily were tried. His behavior did respond to the olanzapine, but the patient developed parkinsonism: a resting tremor was noted on the left more so than right upper extremity. Cogwheeling was present at both wrists. He also had mild bradykinesia. The patient had also been exhibiting some day/night confusion. Trazodone 100 mg was started, in hope of consolidating sleep and avoiding the extrapyramidal side effects of olanzapine. At around the time that he switched to trazodone, the patient wandered 6 miles from home and was frightened enough by his experience with the police that he did not leave home by himself afterwards.

Neuroimaging

An MRI of the brain at 10 years showed severe atrophy of both temporal lobes and mild to moderate atrophy in frontal and insular regions (see Figure 1). A SPECT scan of the brain ordered by the treating neurologist for diagnostic purposes was performed one year into illness showed no significant abnormalities. A PET scan of the brain at 3 years showed severe left temporal lobe hypometabolism and moderate right temporal hypometabolism, mild widening of the longitudinal intercerebral fissure, and increased separation between the caudate heads. Repeat SPECT scan at 5 years showed the prior deficits plus significant left greater than right orbito-frontal and parietal hypoperfusion. Another SPECT scan at 8 years showed further decrease in perfusion. Because dorsal posterior parietal and anterior portions of the intrahemispheric fissure were now involved, clinicians agreed that an atypical temporal variant of Alzheimer's disease could not be ruled out.

Neuropathology

The patient died at home of unstated causes 14 years after onset of illness. His body by that time was markedly cachectic. His family submitted him for autopsy restricted to examination of the brain, which was carried out after a post-mortem interval of approximately 2 hours. Fresh brain weight was 1030 grams. Negligible atherosclerosis was noted in the basal vessels. The brain showed pronounced gyral atrophy, affecting frontal and temporal lobes symmetrically, with questionable relative sparing of the left superior temporal gyrus, i.e. a pattern suggestive of Pick's disease. Severe gyral atrophy was also noted in the cingulate gyri, corpus callosum and hippocampi. The basal ganglia were remarkable for atrophy of the caudate nuclei. Coronal sections of the brainstem and midand parasagittal sections of cerebellum were normal. There was relative sparing of parietal and occipital lobes. There was at most slight atrophy of the pons.

Pick bodies were not present, despite the gross appearance suggestive of Pick's Disease. Marked neuronal loss with astrocytic gliosis and focal spongy change in neocortex was seen on H & E stain, especially involving superficial cortex of the frontal and temporal lobes and

insular neocortex (Figure 2). Neuron loss and pronounced gliosis in the inferior basal ganglia were also seen.

There was minimal Alzheimer type pathology of the brain, with sparse diffuse A-beta 1-42 immunoreactive cortical deposits on immunohistochemistry and negligible neuritic plaques. There were rare tau-immunoreactive neurons in the hippocampal pyramidal cell layer but not the granule cell layer. Significant neocortical tau immunoreactivity and significant amyloid angiopathy were not found.

The substantia nigra was well-pigmented without Lewy Bodies per alpha-synuclein immunohistochemistry. Scattered rod-like or axonal/dendritic ubiquitin immunoreactivity (“ubiquitin neurites”) were widespread throughout neocortex, including the insular cortex. There were rare cells (including scattered neurons) with cytoplasmic TDP-43 immunoreactivity and a ‘neuritic’ pattern of ubiquitin immunoreactivity was noted in many cortical regions, including the insular cortex (Figure 3).

Discussion

This patient had an early-onset dementia that began with features of svPPA and then evolved into marked impairment of interpersonal conduct that can be summarized as marked compulsions (toothbrushing, counting, noseblowing), loss of personal hygiene, and apathy. These behavioural disturbances occurred over a longer period of time than previously reported as mean survival for frontotemporal dementia syndromes.⁷⁻⁹

The case history presented here diverges somewhat from sv-PPA cases appearing in the literature,¹⁰⁻¹³ in that there were significant behavioural disturbances noted even early in presentation, which may be supported by the finding of the severe insular atrophy at autopsy. Pereira et al. report that distinct insular atrophy more frequently accompanies a progression through the progressive non-fluent aphasia subtype of FTD, as opposed to sv-PPA or bvFTD.¹⁴

In behavioral variant FTD, the Salience Network appears to be anchored by the right anterior insula. {Zhou, 2010 #565;Farb, 2011 #2303} Though Seeley et al. report reduced connectivity in regions throughout the network, bvFTD clinical severity correlated with disruption of connectivity between the right frontal pole and the -insula alone.¹⁵ Though semantic dementia and bvFTD differ in their overall patterns of atrophy, both commonly share prominent insular atrophy early in illness.¹⁶ Semantic dementia is typically associated with temporal (left > right), anterior insular and posterior temporal cortical atrophy,¹⁷ while bvFTD is more associated with the ventromedial frontal cortex, posterior orbital frontal regions, left anterior cingulate, the insula bilaterally, right dorsolateral frontal cortex and the left premotor cortex.¹⁶

The insular cortex in this individual was striking for the degree of neuronal loss and astrocytic gliosis, scattered ubiquitin-immunoreactive ‘neurites’, and rather abundant cells (mainly neurons) showing the characteristic cytoplasmic TDP-43 immunoreactivity in the absence of nuclear staining beyond the other regions of the brain, including the left anterior temporal lobe. As reported by Zhou et al., VEN and fork cells populating layer V of the anterior insula seem particularly vulnerable to TDP-43 accumulation.¹⁸

Per previous studies linking OCD and the insula, this patient's dominant obsessive-compulsive features and abnormal eating habits may have related to this regional focus of his pathology.^{5, 19} Seeley's 2010 review of the anterior insula listed lack of empathy and interpersonal warmth as behaviours affected in frontoinsula damage. Both of these were certainly present in the patient even early in illness when his deficits were still largely

semantic in nature. Injury to the right frontoinsula could have caused both his overeating and early disinhibited behaviours, though it is true that injury to lateral orbitofrontal cortex could also have produced these changes.¹⁵ While he did lose emotional processing, it is unclear how much his aphasia contributed to this difficulty, and the severity of this impairment did not seem to differ more than other cases of sv-PPA with less insular involvement.

It is difficult to identify autonomic correlates to the insular atrophy: the patient did not have hemodynamic instability. That he had hyperhydrosis as an adverse effect of most psychotropic medications is difficult to link to the insular atrophy with certainty. Galvanic responses to emotional stimuli might have revealed an abnormality in limbic emotional processing.

Selective serotonin reuptake inhibitors (SSRIs) were prescribed to this patient for symptomatic treatment. Prior experiments have shown that SSRIs can mediate and normalize insular function.^{20, 21} SSRIs did not effectively reduce symptoms of obsessive-compulsive behaviours or emotional blunting in the patient reviewed in this paper, but it is possible that loss of VEN in his insula prevented the SSRIs from having sufficient target substrate.

Conclusion

This case of sv-PPA provides evidence to support Seeley et al.'s hypothesis that VEN and fork cell-rich brain regions, perhaps especially the insula, are targeted in FTD due to TDP-43-opathy.

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Figure 1.

T1-weighted coronal section MRI at 10 years into illness shows marked temporal greater than frontal atrophy, as well as insular atrophy. The atrophy is also asymmetric, worse on the right than on the left. Also note involvement of the hippocampi.

Figure 2.

H and E stained sections of insular cortex from an individual with no neurocognitive abnormalities, photographed at low (a1) and high (b1) magnification. Center panels a2 and b2 show insular cortex from a patient with Alzheimer disease. Panels at right (a3 and b3) show insular cortex from the patient described in this case report, with most marked neuron loss and pronounced astrocytic gliosis.

Figure 3.

Sections of insular cortex from patient described in this case report. Note occasional plaque-like distribution of tau-immunoreactive neurites, a rare finding within the cortex (a), thread-like ubiquitin-immunoreactive processes in the neuropil throughout all cortical regions (including insula) (b,c) and prominent TDP-43 immunoreactivity of cytoplasmic inclusions, apparently within neuronal cell bodies (d).