NEUROLOGICAL RARITY

Semantic dementia: losing the meaning of everything

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INTRODUCTION

Semantic dementia is one form of fronto-temporal dementia (or 'fronto-temporal lobar degeneration'). Fronto-temporal dementia is the second most common cause of dementia in people under 65 years of age, the prevalence in a recent Cambridge series being about 15/100 000; semantic dementia accounts for a substantial minority of these cases. Over the past decade we have seen 75 patients with this condition. We will describe a typical case, focusing on the features of clinical interest; first, the initial presentation and language impairments, followed by the progression of the case and the impairments in other cognitive domains, and concluding with a summary of the neuropathology and prognosis.

A TYPICAL CASE OF SEMANTIC DEMENTIA: FIRST PRESENTATION

This lady was in her fifties when she presented to the Cambridge Memory Clinic complaining of 'memory problems,' which had been gradual in onset and progressively worsening over the previous 12 months. The first problem had been finding the words for the contents of the food trolley in the nursing home where she worked. She had also noticed difficulty in remembering the names of friends, famous people, and even family members. There was no problem with day-to-day memory, nor with autobiographical memory. Her family reported no personality change or odd behaviour, and she was functioning normally in terms of practical skills and daily living. There was no relevant personal or family medical history.

Neurological examination was normal. She was fully oriented and rapidly learned her way around the ward where she had been admitted for investigation. Her conversational speech was fluent and superficially normal, with intact rhythm and melody, accurate articulation, and correct pronunciation and grammar. However, her complaint of word-finding difficulty was borne out in her speech, which showed circumlocution and a tendency to use generic words, such as 'thing', rather than specific terms.

She had great difficulty with object and picture naming, and made errors which were similar in meaning to the target word ('horse' for 'elephant'). When asked to name as many animals as she could, she could think of only five in a minute (normal subjects can name 15–20), but she was better at generating words from a given initial letter. Her comprehension of speech was normal on a conversational level, and she could follow complex commands easily, but her understanding of individual words was impaired on a word–picture matching task. She could read aloud fluently, but made mistakes on words with irregular spelling, pronouncing them as they were written, e.g. 'pint' rhyming with 'mint'. Formal tests of memory were normal for non-verbal material, but word-list learning and other measures of verbal memory were impaired.

EARLY CLINICAL FEATURES OF SEMANTIC DEMENTIA

At her first presentation to clinic, this patient displayed the typical features of early semantic dementia. 'Loss of memory for words' is generally the presenting complaint, and anomia is the most

salient clinical deficit. This occurs insidiously, in the sixth or seventh decade of life, initially with otherwise preserved cognition and normal everyday functioning. The word-finding difficulty often extends to proper names, and there may be associated difficulty recognizing faces (progressive prosopagnosia), especially in those with substantial right temporal lobe atrophy.

The social and structural aspects of language are spared, so casual conversation with the patient may give an erroneously favourable impression of their language ability. Errors in speech take the form of semantically related words ('apple' for 'orange'), or circumlocutions ('play music with it'). One of the most consistent features is the replacement of specific terms by higher-level words ('animal' or 'creature' for 'dog'), even when the target word is more common than its replacement. The accompanying impairment in single-word comprehension is most easily brought out by asking the patient for the definition of a slightly unusual word, such as 'aubergine' or 'caterpillar'. This elicits either a blank look, or an over-generalized description lacking in specific details. The syndrome of surface dyslexia, making the regularization errors described above in reading irregular words, is seen in most cases.

The family may report behavioural features recalling those of frontal-variant fronto-temporal dementia, especially apathy, irritability, disinhibition and change in eating habits. Normal performance is usually seen on formal tests of anterograde and retrograde memory, visuosperceptual and constructional abilities, attention and executive functions, as long as the materials used are not heavily dependent on language. Low scores may be found using verbal tests or complicated verbal instructions, giving a misleading impression of global cognitive impairment.

PROGRESSION AND NON-VERBAL SEMANTIC DEFICITS

Initially, our patient's impairments had appeared to be confined to the area of language. Indeed, these language impairments continued to progress, although her speech remained grammatically and phonetically normal. It became increasingly difficult for her to express specific thoughts, and her speech eventually became almost empty of content or meaningful words, dominated now by 'thing', 'person', 'do', 'go' and similar words. When one of our colleagues said to her, 'We'll see you in a few months', she replied, 'Yes, I come every few, er, things, don't I?' unable to retrieve the word 'months' despite having heard it seconds before. Later still, she was only able to speak in stereotyped expressions – 'special place', 'those bits'.

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Figure 1 An item from the Pyramids and Palm Trees test. Which of the two lower pictures matches the top picture?

However, it became clear that her problems involved more than her speech. Like other semantic dementia patients, she started to show impairment on non-verbal semantic tests. In the Pyramids and Palm Trees test (Fig. 1), the patient chooses which of a pair of pictures matches a third: for example, a palm tree and a fir tree, compared with an Egyptian pyramid. This tests conceptual knowledge without relying on language for understanding or responding. She was also impaired on other non-verbal tests such as matching sounds to pictures. Her understanding of the significance and use of objects also deteriorated; she was unable to demonstrate how to use a can-opener or a screwdriver. She continued to function relatively well at home because she was able to recognize and use her own objects, but she could not generalize to the slightly different ones she was given in clinic.

These developments illustrate the nature of the fundamental deficit in semantic dementia; gradual erosion of the database that gives meaning to sensory experiences, a breakdown of the associations between and within concepts. As the links

become weaker, categories merge and become progressively more generalized and stereotyped. For example, patients are able to copy a drawing of a duck accurately, but when the original drawing is taken away, their delayed copy loses specific features and becomes more like a stereotypical animal, to the extent of acquiring four legs.

Words are usually first and most severely affected, because the link between a word and its associated concept is arbitrary. Someone seeing a hammer for the first time could perhaps work out its use from the shape of the handle and the head, but the sound of the word 'hammer' gives no clue about what it refers to. Semantic dementia patients come to rely heavily on their intact perceptual and motor skill; they can recognize their own comb and know what to do with it, but cannot recognize that a slightly different-looking object is also a comb and can be used as such. Food is often a particular problem; one patient for example poured orange juice on his lasagne and proceeded to eat it without realizing that anything was amiss.

PATHOLOGY

Asymmetrical antero-inferior temporal lobe atrophy is the rule in semantic dementia. This is easily missed on CT but is better detected by coronal MRI (Fig. 2). Volumetric MRI measures demonstrate some involvement of both hemispheres, but individual cases usually show left-sided emphasis, with a minority of right-predominant cases. Recent studies point to a

Figure 2 Coronal MR scan of a semantic dementia patient. Note the striking temporal lobe atrophy, worse inferiorly and on the left (arrowed).

There is gradual erosion of the database that gives meaning to sensory experiences, a breakdown of the associations between and within concepts.

SUMMARY POINTS

- Semantic dementia should be suspected when a patient in late middle-age complains of 'loss of memory for words' or progressive word-finding difficulty, and their speech is fluent and accurate but lacking in content.
- Impairments may be brought out by picture or object naming, naming to description (and describing from the name) and category fluency ('how many animals can you name in a minute?').
- Formal neuropsychological assessment shows anomia and single-word comprehension impairment, often with surface dyslexia, and intact syntax, phonology, episodic memory, non-verbal perception and problem-solving skills.
- Asymmetrical temporal lobe atrophy is seen on imaging.
- The prognosis is variable, but progression to death normally occurs over a few years.
- Management consists of explanation and support for the patient and carers.

key role for the perirhinal cortex. Patients with left-predominant atrophy tend to show more language difficulty, whereas right-sided atrophy is associated with progressive prosopagnosia, altered social behaviour and poor insight.

The inclusion of semantic dementia under the broad heading of fronto-temporal dementia is justified by:

- the overlap of behavioural features with frontal-variant fronto-temporal dementia;
- the distribution of atrophy in the frontal and temporal lobes;
- the group of pathological findings which underlie both.

The characteristic histopathology of fronto-temporal dementia is neuronal loss leading to

cortical spongiosis and gliosis. This may be associated with neuronal inclusions with specific immunohistochemical characteristics, for example tau-positive Pick bodies. Tau-negative but ubiquitin-positive inclusions (Fig. 3) are seen in fronto-temporal dementia associated with motor neuron disease (MND), but may occur in any subtype of fronto-temporal dementia, with or without clinical MND. Recent studies indicate that MND-type ubiquitin-positive inclusions are the most common pathology in semantic dementia, and was indeed the pathology in the case we described, who died 13 years after her initial presentation.

PROGNOSIS

Our recent collaborative series from Cambridge and Sydney examined survival data in fronto-temporal dementia subtypes. The median survival was 8 years from the onset of symptoms. Owing to the preservation of social conduct and activities of daily living, semantic dementia tends to present later than most other dementias, but median survival from diagnosis was only 3 years. These figures mask very wide variation in the rate of progression, and some patients have survived for 10 years or more after diagnosis, as with our case. There is no pharmacological treatment for the symptoms or the underlying condition, and the results of memory or cognitive re-training in degenerative syndromes are generally poorer than in rehabilitation from discrete lesions.

FURTHER READING

- Hodges JR, Patterson K, Oxbury S & Funnell E (1992) Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain*, **115**, 1783–806.
- Thompson SA, Patterson K & Hodges JR (2003) Left/right asymmetry of atrophy in semantic dementia: behavioral-cognitive implications. *Neurology*, **61**, 1196–203.

Figure 3 Hippocampal dentate gyrus from a semantic dementia patient, magnification $\times 400$, stained with haematoxylin and antiubiquitin antibody. Note the densely staining ubiquitin-positive intraneuronal inclusions.