Semantic dementia: demography, familial factors and survival in a consecutive series of 100 cases

John R. Hodges,1,2 Jo Mitchell,2 Kate Dawson,2 Maria Grazia Spillantini,2 John H. Xuereb,3 Paul McMonagle,3 Peter J. Nestor2 and Karalyn Patterson4

1 Prince of Wales Medical Research Institute (POWMRI), University of New South Wales, Randwick, Sydney, NSW 2031, Australia
2 University Department of Clinical Neurosciences, Addenbrooke’s Hospital, Cambridge, UK
3 Department of Pathology, University of Cambridge, UK
4 MRC Cognition and Brain Sciences Unit, Cambridge, UK

Correspondence to: Prof. John R. Hodges,
Prince of Wales Medical Research Institute,
Cnr Barker & Easy Street,
Randwick, NSW 2031,
Sydney,
Australia
E-mail: j.hodges@powmri.edu.au

A great deal has been written about cognitive aspects of semantic dementia but little is known about the demography or prognosis. We describe these features in a consecutive series of 100 patients seen over a 17-year period; all cases were assessed and followed up in a specialist clinic. The mean age at diagnosis was 64.2 (±7.1) range 40–79 years, but 46 presented after age 65 and 7 after 75; a higher proportion than the existing literature might predict. Fifteen had a first-degree relative with dementia, but in seven this was almost certainly unrelated. Only two had relatives with young-onset dementia. There were no families with more than two affected members. The familial rate was estimated at between 2% and 7% (95% confidence interval 0–12%); a more benign course than suggested by neuropathologically based studies. We were unable to identify any factors influencing survival. Of the 100, 34 have died, with pathological confirmation in 24; 18 had frontotemporal lobar degeneration with ubiquitin-positive inclusions (13 of 13 confirmed TAR DNA binding protein-43 positive), and 3 had classic tau-positive Pick bodies and 3 had Alzheimer’s pathology. The age at diagnosis or death across the pathological subgroups was equivalent. Although semantic dementia has a strong statistical association with ubiquitin-positive pathology, it does not have the signature of familial frontotemporal lobar degeneration with ubiquitin-positive inclusions, notably the presence of intranuclear lentiform TAR DNA binding protein-43 inclusions. The age of onset is older than predicted and the course more slowly progressive than suggested by earlier studies of small groups of subjects.

Keywords: frontotemporal dementia; semantic dementia; ubiquitin pathology; TDP43

Abbreviations: ACE = Addenbrooke’s cognitive examination; CDR = clinical dementia rating; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; FTLD-tau = classic tau-positive Pick body frontotemporal dementia; FTLD-U = frontotemporal lobar degeneration with ubiquitin-positive tau-negative inclusions; MMSE = mini-mental state examination; NPI = the neuropsychiatric inventory; TDP = TAR DNA binding protein

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Introduction

The syndrome of semantic dementia has been of considerable interest to behavioural neurologists and neuropsychologists since it was first described 100 years ago (Pick, 1892, 1904; Rosenfeld, 1909). In the modern era, interest was re-awakened following Warrington’s (1975) seminal description of three patients with a combination of visual associative agnosia, anomia and disrupted comprehension of word meaning which Warrington conceptualized as secondary to a fundamental breakdown in semantic knowledge (Tulving, 1972). Other cases were subsumed under the label of primary progressive aphasia (Mesulam, 1982, 1987); but the disorder became increasingly recognized as a specific clinical syndrome following the report by Snowden and colleagues (1989) in which they coined the term ‘semantic dementia’. Our paper in 1992 proposed criteria for semantic dementia and made the association between the clinical features and bilateral but asymmetric atrophy of the anterior temporal lobes (Hodges et al., 1992). Over the past 15 years, numerous studies have clarified the clinical neuropsychological features of the syndrome and the implications for understanding cognitive architecture and the neural basis of semantic memory (for review, see Westbury and Bub, 1997; Grossman and Ash, 2004).

From a nosological perspective, semantic dementia is now regarded as one of the three main clinical variants of fronto-temporal dementia (FTD), sometimes also referred to as fronto-temporal lobar degeneration (FTLD) (Neary et al., 1998); the other two are progressive non-fluent aphasia and the behavioural variant of FTD. The neuropathological findings in FTD are varied with a range of tau-positive and tau-negative changes (Hodges et al., 2004; Mackenzie et al., 2006a, b). Recent work has established that the majority of patients with semantic dementia have ubiquitin-positive, tau-negative intraneuronal inclusions, although occasional cases have classic tau-positive Pick body pathology and a few have Alzheimer’s disease with an atypical distribution of pathology (Davies et al., 2005).

In contrast to the extensive cognitive literature on semantic dementia, surprisingly little has been published related to its demography and prognosis. Regarding age of onset, it is commonly held that semantic dementia, in line with other forms of FTD, is a ‘pre-senile’ disorder with onset between the ages of 45 and 65 years. Recent clinicopathological and clinical studies have, however, reported onset after 65 years in 20%-40% of FTD cases (Gislason et al., 2003; Harvey et al., 2003; Ibach et al., 2003, 2004). Reports based on post-mortem series suggested a median survival in semantic dementia of ~8 years, range 3–15 (Hodges et al., 2003), but this figure was based on a relatively small sample size (n ≤ 20) and may have been biased by the restriction to patients reaching autopsy.

Another topic of interest is the extent to which semantic dementia is familial. There have been considerable advances in understanding the genetics of FTD with the discovery of two major gene defects (on MAPT and progranulin, both on chromosome 17) plus 2 much rarer loci (CHMP2B and valosin) in familial FTD (Goedert et al., 1998; Skibinski et al., 2005; Baker et al., 2006; Cruts et al., 2006; Gasparini et al., 2007; Guinto et al., 2007).

Taking FTD as a whole, up to 40% of cases are said to have a positive family history of a neurodegenerative disorder, but in many instances this is probably incidental. Cases with a strong familial tendency (a clear FTD syndrome and/or early-onset dementia in one or more first-degree relatives) are much rarer, perhaps accounting for 10%-20% (Rosso et al., 2003a, b). Moreover, the familial rate appears not to be equally distributed across FTD subtypes. A collaborative cross-centre study from the USA reported a much lower familial rate in semantic dementia compared with other clinical FTD variants (Goldman et al., 2005). This important observation clearly requires further investigation.

The aim of the present study was to report the demographic findings on a consecutive series of 100 semantic dementia cases seen over the past 17 years in Cambridge; with an emphasis on the age of presentation, sex distribution and survival. In all patients, we have enquired in detail concerning a potential family history. All patients have been followed up in a specialist clinic until institutionalized, or deceased, allowing us to report on survival and possible presenting factors which might influence prognosis.

Methods

The Memory Clinic in Cambridge, UK, was established in 1990 and, from its inception, all cases were classified and recorded on a diagnostic database. In total, between 1990 and 2007, we assessed 3600 new patients in the Memory Clinic, with approximately half of referrals coming from other specialists (neurologists and psychiatrists) and half from general practitioners (GPs) in East Anglia. A final diagnosis of dementia was made in half of these cases, with 416 given a diagnosis of focal cortical dementia: 128 behavioural variant FTD, 110 semantic dementia, 66 progressive non-fluent aphasia, 36 mixed aphasic/behavioural cases and 66 with corticobasal syndrome. All patients with focal cortical syndromes were followed up in a dedicated early onset dementia clinic. As part of the clinic protocol, all patients (with the help of their caregiver) were asked to complete a life and family history questionnaire, developed in Cambridge, prior to their first attendance at the clinic; this enquired about the health and causes of death of all first-degree relatives and, in particular, a history of dementia, Parkinson’s disease, motor neurone disease or major mental health problems. Patients with any positive endorsement of these items were then questioned to obtain further details. All data were entered on the clinic database.

Of the 110 with a diagnosis of semantic dementia, 10 were excluded because the data were too limited: the patient either presented at a very advanced stage and therefore had limited follow-up (n = 7) or came from (and returned to) a country other than UK (n = 3). Of the final semantic dementia cohort, 68 were referred by the specialists and 32 by the GPs. We estimated, therefore, that we made a diagnosis of semantic dementia in 4% of the specialist and 1.8% of the GP referrals to our memory clinic. If the rate is calculated only from those diagnosed with dementia, then 8% of the specialist and 3.6% of the GP referrals had semantic dementia. Every effort was made to remain in contact with semantic dementia...
patients and their families even when they were no longer able to
attend the clinic, and also to enrol cases as potential donors in our
Brain Bank Programme, particularly after 1997. Of those with a
declaration of intent in vivo, our rate of obtaining brain tissue
post-mortem has been >90%. Many of the patients have been
included in cognitive imaging or neuropathological reports which
have spanned the past 15 years.

In all patients identified as semantic dementia, the main present-
ing pattern was either (i) progressive deterioration of both expressive
and receptive vocabulary in the context of relatively fluent and
phonologically correct speech production, together with impaired
performance on tests of non-verbal semantic knowledge—the classic
profile associated with left-predominant temporal lobe atrophy; or
(ii) progressive impairment in recognition of people of a cross-
modal type affecting identification of faces and names, plus
impaired performance on tests of verbal and non-verbal semantic
knowledge—a profile which typifies those with right-predominant
atrophy (Thompson et al., 2003). All patients showed preservation
of day-to-day memory and orientation, working memory, visuospatial
and perceptual abilities and non-verbal problem-solving skills
(Hodges et al., 1992; Adlam et al., 2006a, b). Structural imaging
by MRI revealed focal atrophy in one or both anterior temporal
lobes (Galton et al., 2001; Davies et al., 2004; Galton et al.,
2001; Williams et al., 2005). In total, 94 patients had MRI
scanning (the other six had CT only, for a variety of reasons).
In all 94, sufficient information was available on the distribution
of the anterior temporal atrophy to allow classification as left- or
right-predominant atrophy.

All patients underwent a detailed neuropsychological evaluation
with tests designed to assess the following domains: semantic
memory (category fluency, picture naming, word–picture matching
and picture–picture associative tasks using the Cambridge Semantic
Battery) (Bozeat et al., 2000; Hodges and Patterson, 2007), verbal
and visual episodic memory, working memory, problem solving,
visuospatial and visuoperceptual abilities. The exact tests changed
somewhat over the 17 year period of case acquisition and the results
will not be reported here: most of these findings have been published
elsewhere. All patients had the mini-mental state examination (MMSE)
and, after 1997, the Addenbrooke’s Cognitive Examination (ACE)
(Mathuranath et al., 2000; Mioshi et al., 2001; Davies et al.,
2000, 2004; Galton et al., 2001; Williams et al., 2005). A carer-based
schedule, the Clinical Dementia Rating (CDR), was used to assess
the severity of impairment in everyday skills. The Neuropsychiatric
Inventory (NPI: Cummings, 1997), introduced in 1997, was completed
for 73 patients.

## Results

### Demographic and clinical data

Of the 100 cases, 60 were men and 40 women. They were a
relatively well-educated group with a mean of 12.3±2.9 years
full-time education: 38 had a professional background, 28 were
skilled workers, 16 semi-skilled and 14 manual workers (we failed
to obtain occupational information for n = 3).

The mean age at onset of symptoms, as related by family
members, was 60.3 (±7.1) years with a range of 40–79 and the
mean age at diagnosis was 64.2 (±7.1), indicating an average lag
of 4 years between symptom onset and diagnosis (Table 1).
As shown in Fig. 1, the modal age for diagnosis was between
60 and 64 years. Only one patient was aged under 50. Of note
was the fact that in 46 patients, the diagnosis was made after the
age of 65 years, in 7 after 75 years and in 1 after 80 years. The
mean MMSE at presentation was 21.0 (±4.4) and the CDR score
0.76 (±0.5). There was a modest endorsement on the NPI

![Figure 1 Distribution of age at diagnosis for all 100 semantic dementia cases.](https://academic.oup.com/brain/article-abstract/133/1/300/309049)

**Table 1 Comparison of basic demographic data of the 94 cases with a known pattern of atrophy on MRI**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole group</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>60/40</td>
<td>38/32</td>
<td>18/6</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.3±2.9</td>
<td>12.4±3.1</td>
<td>11.6±2.4</td>
</tr>
<tr>
<td>MMSE</td>
<td>21.0±6.4</td>
<td>20.2±6.67</td>
<td>24.0±4.6</td>
</tr>
<tr>
<td>CDR</td>
<td>0.8±0.5</td>
<td>0.7±0.5</td>
<td>0.7±0.5</td>
</tr>
<tr>
<td>NPI (n=73)</td>
<td>20.4±16.5</td>
<td>18.2±15.5</td>
<td>26.4±18.0</td>
</tr>
<tr>
<td>Age at onset</td>
<td>60.3±7.01</td>
<td>60.3±7.1</td>
<td>59.3±6.5</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>64.24±7.1</td>
<td>64.5±7.2</td>
<td>63.1±6.6</td>
</tr>
<tr>
<td>Age into NH (n=30)</td>
<td>66.9±6.5</td>
<td>67.0±6.4</td>
<td>66.6±7.1</td>
</tr>
<tr>
<td>Age at death (n=32)</td>
<td>69.7±5.8</td>
<td>69.5±5.6</td>
<td>70.1±6.6</td>
</tr>
<tr>
<td>50% survival (95% CI)</td>
<td>12.7 (11.9–13.7)</td>
<td>13.0 (11.9–14.1)</td>
<td>11.7 (10.3–13.4)</td>
</tr>
<tr>
<td>Median survival</td>
<td>14.0 (12.5–15.5)</td>
<td>14.0 (12.8–15.2)</td>
<td>12.0 (9.8–14.2)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
typically involving apathy and repetitive behaviours with a mean score of 20.4 (±16.5).

Table 1 compares basic demographic data of the 94 cases with a known pattern of atrophy on MRI. Of these 94 cases, 70 had left- and 24 right-predominant atrophy. The sex distributions, years of education, ages at onset and at diagnosis were almost identical in the two subgroups. The MMSE was higher in the right-predominant group (24.0 ± 4.6 versus 20.2 ± 6.7) but the difference did not reach significance. The right group had higher scores on the NPI (26.4 ± 18.0 versus 18.2 ± 15.5) indicating a greater incidence of neuropsychiatric symptoms, but this difference also did not reach significance.

Family history
A family history was taken in all 100 cases as described earlier: 15 had a family history of dementia in a first-degree relative. In 7 of the 15 cases, there was sufficient evidence to make an alternative diagnosis outside the FTD spectrum including vascular dementia, alcoholism and longstanding Parkinson’s disease. In the remaining 8, a diagnosis of Alzheimer’s or senile dementia had been made, but information on these family members was relatively scanty as most had died many years before. In one patient, we were able to obtain post-mortem confirmation that his mother had Alzheimer’s disease with an onset in her seventies, leaving seven possible familial cases. Only two patients (2%) had a clear family history of early onset dementia or ‘Pick’s disease’ but without pathological confirmation in either instance. There were no families with more than two affected members. The rate of a suggestive family history was, therefore, between 2% and 7% (95% confidence interval (CI) 0–12%).

Survival analyses and pathology
To date, 32 of the 100 patients have died at a mean age of 69.7 ± 5.8 years. Pathological confirmation was available in 24 of the 32: 18 had FTLD with ubiquitin-positive tau-negative inclusions (FTLD-U), 3 had classic tau-positive Pick body FTD (FTLD-tau) and 3 Alzheimer pathology: 18 of the 24 cases were included in a prior study by Davies et al. (2005). The pattern of ubiquitin-positive staining corresponded to type 2 in the Mackenzie et al. (2006) classification, with ubiquitin-positive neurites in layer II of the cortex and in the dentate gyrus but without intranuclear ‘cat’s eye’ inclusions. Of the 18 with ubiquitin-positive inclusions, we were able to retrieve sufficient material to re-stain for TAR DNA binding protein (TDP)-43 in 13 cases. In brief, 8 μm paraffin sections were rehydrated and boiled in 10 mM trisodium citrate–HCl buffer pH 6 for antigen retrieval. Sections were incubated overnight at 4°C with primary antibody polyclonal antiserum anti-TDP43 (1:2000; ProteinTech Inc.). Staining was developed using the Vectastain biotin–avidin ABC Elite Kit (Vector Laboratories) and visualized using 3,3’-diaminobenzidine (DAB) as substrate (Vector Labs). Sections were counterstained with cresyl violet, all of which were positive. Usually round or curved cytoplasmic TDP43 inclusions were present in the dentate fascia of the hippocampus. Similar inclusions and TDP43 dystrophic neurites were present in frontal and mainly in temporal cortices. Representative illustrations of TDP43 staining of the dentate gyrus and frontal cortex are shown in Fig. 2.

The age at diagnosis and death was equivalent across the three pathological subgroups: FTLD-U 63.5 and 71.5 years; FTLD-tau 65.3 and 69.6 years; Alzheimer’s disease 67.2 and 71.5 years, respectively. Of note is the fact that our oldest patient, who presented at the age of 77 years and died at the age of 88 years, had FTLD-U as did four others diagnosed in their seventies. One patient with a presentation in their 70s had FTLD-tau. The three patients with Alzheimer’s disease pathology were aged 60, 63 and 79 at the time of diagnosis and died aged 64, 66 and 85. Review of clinical, neuropsychological and imaging data revealed no consistent differences between the pathological subgroups.

Of the surviving 68, 34 are in institutional care and 34 are living at home and under follow-up in the clinic.
A total of 32 patients have died and we obtained post-mortem confirmation of the pathological diagnosis in 24: 18 had FTLD with ubiquitin-positive tau-negative inclusions (FTLD-U), 3 had classic tau-positive Pick body FTLD and 3 Alzheimer pathology. These findings extend a prior report on 18 semantic dementia cases (Davies et al., 2005). The genetic influence on the aetiology of semantic dementia appears to be low. In our cohort, 15% reported a first-degree relative with dementia, but in seven cases this was almost certainly unrelated and one had pathologically confirmed Alzheimer’s disease. Only two had relatives with early onset dementia and there were no multiplex families. Bearing in mind the late onset of many of our cases, it is possible that a proportion of the elderly relatives diagnosed as Alzheimer’s disease might have had semantic dementia. Even with this proviso, the maximum rate of positive family history was 7% (95% CI 0–12%).

As discussed earlier, FTD is generally regarded as a pre-senile dementia syndrome. Research has identified FTD as the second commonest neurodegenerative cause of dementia in the under 65s (Ratnavalli et al., 2002) with a prevalence in that age range which approaches that of Alzheimer’s disease. This study suggests that it might, in fact, be a significant cause of dementia in those diagnosed beyond 65. Of note is the fact that in six patients presenting over the age of 70 years, we have pathological confirmation of an FTLD syndrome (5 FTLD-U and 1 FTLD-tau). In contrast of the three with pathological Alzheimer’s disease, two were aged under 65 and one was 79-years old. There seems no way, therefore, of predicting pathology on the basis of age.

Estimates based on specialist clinics are, of course, open to bias. The 100 semantic dementia patients reported here represent a quarter of all those with FTD syndromes which, in turn, was the diagnosis in 20% of 1800 patients with dementia seen over a 17 year period. Since the primary complaint of most semantic dementia patients is ‘loss of memory’ and they perform poorly on tests of verbal episodic memory—which forms the mainstay of dementia screening tests—it is easy to imagine why patients could be diagnosed with Alzheimer’s disease unless fuller neuropsychological testing and/or magnetic resonance imaging (MRI) are performed. Clues to the diagnosis, on the positive side, are well-preserved orientation, excellent visuospatial skills and good non-verbal episodic memory; and, with regard to notable impairments, poor category fluency, excellent visuospatial skills and good non-verbal episodic memory; and, with regard to notable impairments, poor category fluency, and word comprehension plus surface dyslexia. This profile has been shown to produce a characteristic pattern of impairment and preservation on the ACE, which is a 15 min cognitive screening tool readily applicable for use in a general memory clinic (Mioshi et al., 2006). Coronal MRI consistently shows anterior temporal lobe atrophy involving the polar, parahippocampal and inferior temporal regions with striking involvement of the anterior fusiform gyrus, a tell-tale sign universally present in semantic dementia (Galton et al., 2001; Davies et al., 2004) that may potentially have diagnostic utility in excluding apparent clinical semantic dementia patients who have Alzheimer pathology (Pereria et al., 2009).

The average delay between symptom onset and diagnosis was 4 years and did not differ between those with predominant right-versus left-temporal atrophy. The preponderance of patients with
left more than right-temporal atrophy was noted by earlier authors (Hodges, 2007), but the cause of this asymmetry has remained mysterious. The findings here that left more than right and right more than left subgroups had similar ages of onset and similar delays between onset and diagnosis, fail to support one previous hypothesis that the deficits of face and voice recognition seen in right-predominant cases are less noticeable to family members than the striking anomia, which characterizes left-predominant semantic dementia (Thompson et al., 2003). The cause for this striking biological asymmetry awaits explanation.

There have been substantial advances in our understanding of the neuropathology and genetics of FTD. Although it is claimed that up to 40% of patients with FTD are genetically determined, a previous multicentre study established very different rates across different syndromes in the FTD spectrum, with a low rate for semantic dementia (Goldman et al., 2005). A large survey from the Netherlands also found a much lower rate of an autosomal dominant inheritance pattern in patients with semantic dementia (4%) compared with those with behavioural variant FTD subtypes (36%) (Seelaar et al., 2008). We have confirmed here that relatively few semantic dementia patients appear to have a significant family history. All patients completed a life and family history questionnaire and in 15 there was a history of dementia in a first-degree relative. In eight of these, we were able to establish an alternative aetiology leaving seven with a possible family history. Only two had a history of younger-onset dementia but given our alternative aetiology leaving seven with a possible family history.

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