The Clinical Spectrum of Young Onset Dementia Points to Its Stochastic Origins

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Abstract

Background: Dementia is a major global health problem and the search for improved therapies is ongoing. The study of young onset dementia (YOD)—with onset prior to 65 years—represents a challenge owing to the variety of clinical presentations, pathology, and gene mutations. The advantage of the investigation of YOD is the lack of comorbidities that complicate the clinical picture in older adults. Here we explore the origins of YOD.

Objective: To define the clinical diversity of YOD in terms of its demography, range of presentations, neurological examination findings, comorbidities, medical history, cognitive findings, imaging abnormalities both structural and functional, electroencephalographic (EEG) data, neuropathology, and genetics.

Methods: A prospective 20-year study of 240 community-based patients referred to specialty neurology clinics established to elucidate the nature of YOD.

Results: Alzheimer’s disease (AD; n = 139) and behavioral variant frontotemporal (bvFTD; n = 58) were the most common causes with a mean age of onset of 56.5 years for AD (±1 SD 5.45) and 57.1 years for bvFTD (±1 SD 5.66). Neuropathology showed a variety of diagnoses from multiple sclerosis, Lewy body disease, FTD-MND, TDP-43 proteinopathy, adult-onset leukoencephalopathy with axonal steroids and pigmented glia, corticobasal degeneration, unexplained small vessel disease, and autoimmune T-cell encephalitis. Non-amnestic forms of AD and alternative forms of FTD were discovered. Mutations were only found in 11 subjects (11/240 = 4.6%). APOE genotyping was not divergent between the two populations.

Conclusion: There are multiple kinds of YOD, and most are sporadic. These observations point to their stochastic origins.

Keywords: Neurodegeneration, sporadic onset, stochasticity, young onset dementia

INTRODUCTION

In the latter 20th century, clinics were established in Perth, Western Australia to elucidate the phenomenology of young onset dementia (YOD) [1]. The clinics were founded to elucidate the causes and natural history of YOD and to serve as a basis for research.

The driving hypothesis was that YOD was genetically driven, distinguishing it from dementia in the elderly.

Over the years we were able to show that Alzheimer’s disease (AD) and frontotemporal dementia (FTD) were the most common neurodegenerative processes; psychiatric diseases were also found in the YOD population, along with obstructive sleep apnea [2]. Our experience confirmed the observations of others [3–7]. We went on to illuminate the significant psychosocial impact of YOD on spouses [8] and to define their needs [9]. We elucidated the natural history in our population showing that patients...
with FTD had a worse prognosis than those with AD [10]. We revealed that cerebrovascular risk factors, such as hypertension and a single apolipoprotein E genotyping (APOE) e4 allele, might be important in the development of young onset Alzheimer’s disease (YOAD) but not FTD [11].

Our studies of larger populations indicated that elevated inflammatory markers, impaired renal function, and APOE e4 alleles are over-represented in late onset AD, inferring biological differences between young and late onset AD [12]. Studies in larger populations disclosed that ethnic minorities, like African Americans, may be of increased risk of developing YOAD [13, 14]. Our investigations evinced that YOAD occurs independently of hypertension, stroke, and atrial fibrillation [14]. Our inquiries revealed that brain FDG-PET imaging might help in the diagnosis of YOAD by increasing positive likelihood rates and post-test probability; the high specificity of the test pointing to its utility in the diagnosis of YOD [15]. We went on to show that an abnormally low cerebrospinal fluid (CSF) Aβ1–42 and elevated P-tau and T-Tau were especially useful in YOAD [16]. Other explorations intimated that cognitive reserve was operational in YOD [17].

Considerations of the contributions of genetic mutations as causes of YOD led us to develop guidelines for gene testing [18] and its utility [19]. Genetic studies in our populations indicated that most did not have a positive family history; that YOD was not strongly inherited as an autosomal dominant trait; and that known mutations were uncommon, occurring in less than 10% of the total study population [20]. These observations led us to ask the question: what drives YOD if most patients are sporadic in origin? This directed us to propose that stochastic mechanisms determine the evolution of YOD [21]. The null hypothesis is stated that young onset dementia is genetic in origin. In this investigation we wish to develop further this concept of stochastic processes by defining the clinical heterogeneity of YOD in our patient population, searching for genetic and other clues as to its origins.

MATERIALS AND METHODS

A prospective 20-year study of YOD was performed in Perth, Western Australia in specialist community-based clinics established by the author allied with The University of Western Australia, devoted to the assessment and care of such patients, and known as the ARTEMIS Project. Patients with the question of YOD were assessed after referral from general practitioners, neurologists, psychiatrists, geriatricians, and other physicians. YOD is defined in this study as dementia onset prior to the age of 65 years. Patients were seen from the beginning to the end and neuropathological examinations obtained wherever possible. Patients, their carers, and their families were seen at least every 6 months and were followed for a median 10 years (3–15 years). Patients were diagnosed by the same neurological team of neurologists, psychiatrists, neuropsychologists, psychologists, and case managers. All patients and their carers gave written informed consent (Ethics approval: JHC HREC: ARTEMIS 1406). Patients were diagnosed using evolving published criteria valid at the time of enrolment. Patient diagnoses and criteria were reviewed at each visit. AD was diagnosed based on the original 1984 NINCDS-ADR A criteria [22]. The diagnosis of dementia was based on cognitive or behavioral symptoms that interfere with the ability to function at work or have a decline from previous function, not explained by psychiatric disease or delirium. Cognitive impairment was diagnosed by history taking from patient and percipient informant and cognitive assessments including: Addenbrooke’s Cognitive Examination – Revised 2005 (ACE-R), Mini-Mental State Examination (MMSE), Total Functional Capacity (TFC), Symbol Digits Modalities Test (SDMT), Depression, Anxiety and Stress Scores (DASS), Frontal Rating Scale (FRS), and the Cambridge Behavioural Inventory (CBI)—the latter two scored by the informant, spouse, or carer. Neuropsychology tests were performed when uncertainty as to the diagnosis persisted. The diagnosis of YOAD refers to probable AD dementia [23]. All our patients had functional decline. None of our patients had mixed presentations, unless stated, such that our population do not have co-existent cerebrovascular, Lewy body, or other neurological processes, including medication side effects. The diagnostic work-up was supplemented by magnetic resonance imaging (MRI) and 18Fluorodeoxyglucose uptake, which enhance the likelihood that our YOAD patients had the AD pathophysiological process. Biomarkers such as low CSF Aβ42 and positive PET amyloid imaging have only become available more recently and were not possible when the study was initiated. Tau PET imaging is not available in Western Australia outside of pharmaceutically funded research. The diagnosis of pathophysio logically proved AD dementia...
is a category for individuals with clinical criteria for dementia proven neuropathologically to have AD, using accepted standards [24]. Patients were classified as having amnestic AD or non-amnestic presentations: linguistic, visuospatial, frontal, or other [25].

Behavioral variant frontotemporal dementia (bvFTD) and its alternatives—primary progressive (non-fluent) aphasia and semantic dementia—were diagnosed using criteria which matured over time [26–29]. None of our patients had a significant burden of white matter changes or stroke to fulfil criteria for vascular cognitive impairment [30].

Prodromal AD was diagnosed by cognitive symptomatology, without functional compromise and FDG-PET evidence of AD pathophysiological change (e.g., precuneus hypometabolism for which no other cause could be identified) [31]. Prodromal AD substituted for mild cognitive impairment. Lewy body disease (LBD) was identified using the McKee criteria [32]. Prion disease was recognized by employing the Zerr standards [33]. Cerebral amyloid angiopathy was determined using the Boston criteria [34]. Progressive supranuclear palsy (PSP) and cortico-basal syndrome degeneration (CBD) are regarded as part of the clinical spectrum of the tauopathies [35–37].

Routine genetic techniques, counselling, and ethical guidelines were used to determine the presence of common genetic mutations in AD, FTD, and prion disease if there was a family history of a first degree relative with dementia to maximize the probability of finding a genetic anomaly [38–40]. APOE genotyping was performed using standard PCR methods [41].

RESULTS

Alzheimer’s disease (AD)

There were 139 people with YOAD with a mean age of onset of 56.5 years (±1 SD 5.45). There was a slightly greater preponderance of females. Most YOAD patients had less than 12 years of education. The majority were married. Most were not overweight. Memory loss was the most common initial manifestation without behavioral change. Cognitive decline was seen. Extrapyramidal dysfunction was infrequently observed. Frontal lobe linguistic presentations, posterior cortical atrophy and progressive apraxia were found in less than 10% of patients. Hyperemotionality and psychomotor slowing were seldom noticed (Table 1).

Hypertension, dyslipidemia, alcoholism, smoking, diabetes mellitus 1 and 2, ischemic heart disease, and obstructive sleep apnea were identified in less than 30% of the population (Table 2).

Cancer was seen in around 10%. The majority of subjects had not had a head injury. Most were righthanded. Over half of the subjects did not have a family history of AD (56.1%). About one-quarter of subjects (23%) had a first degree relative with AD, all of which were old onset; less than a tenth had two first degree relatives with old onset AD (Table 3).

Significant psychosocial stressors (marital, separation, divorce, financial collapse, death of a spouse, suicide of a spouse, moving continents) were observed in about 60% of the YOAD population. At the time of analysis, the majority were at home, almost 30% had died and 15% were in a nursing home (Table 3).

About half had at least one APOE e4 allele (Table 4).

At first contact the mean MMSE was 21.2 (median 23, SD 6.3) and showed progressive deterioration with time—5 consecutive years recorded in Table 5. The ACE-R was also significantly reduced at first presentation and shows worsening with time. Depression, anxiety, and stress were not elevated overall in the population at presentation and on re-testing one year later. The TFC (a measure of the ability to cope) was usually impaired and progressively deteriorated over successive years. The CBI (an eyewitness, usually spouse or partner, account of the patient’s cognition and behavior) was mildly increased and worsened with time over successive years, as did the FRS (an observer measure of frontal lobe function).

The MRI revealed atrophy in about 64% at initial scan at first assessment. The atrophy was frontal in about 11%, global in 8%, temporal in 12%, parietal in 13%, mesial temporal in 8%, and posterior cortical in 1.5% (Table 6).

The electroencephalogram (EEG) showed abnormal slow wave or epileptogenic activity in about 80% of subjects (Table 6).

Abnormal amyloid tracer uptake using PET scanning was found in all patients with YOAD in whom it was measured.

Using FDG-PET imaging, the parietal region was the most commonly affected area with reduced metabolism (93%), followed by the occipital region, temporal, precuneus, frontal and posterior cingulate in that order.
| Demographics | Disease Type | EOAD (amnestic form) | EOFTD (bvFTD) | Diff btw EOAD and EOFTD | Other |
|--------------|-------------|----------------------|---------------|-------------------------|-------|
| Gender       |             | N  | Col % | N  | Col % | N  | Col % | χ² and p | N  | Col % |
| female       |             | 114 | 47.5  | 80 | 57.6  | 19 | 32.8  | 10.1; p = 0.001 | 15 | 34.9 |
| male         |             | 126 | 52.5  | 59 | 42.4  | 39 | 67.2  | 28          |     |
| Education (y) |           | 97 | 40.4  | 53 | 38.1  | 21 | 36.2  | 1.4; p = 0.49 | 23 | 53.5 |
| less than 10 |           | 73 | 30.4  | 47 | 33.8  | 16 | 27.6  | 10          | 23.3 |
| 11–12        |           | 70 | 29.2  | 39 | 28.1  | 21 | 36.2  | 10          | 23.3 |
| Marital status |         |    |       |    |       |    |       | 2.1; p = 0.15 | 8  | 18.6 |
| No           |           | 44 | 18.3  | 29 | 20.9  | 7  | 12.1  | 35          | 81.4 |
| Yes          |           | 196| 81.7  | 110| 79.1  | 51 | 87.9  | 8           | 14.0 |
| Overweight   |           | 208| 86.7  | 125| 89.9  | 46 | 79.3  | 4.0; p = 0.04 | 37 | 86.0 |
| No           |           | 32 | 13.3  | 14 | 10.1  | 12 | 20.7  | 6           |     |
| Yes          |           | 171| 71.3  | 123| 88.5  | 28 | 48.3  | 20          |     |
| Memory loss  |           | 69 | 28.8  | 16 | 11.5  | 30 | 51.7  | 37.0; p < 0.001 | 23 | 53.5 |
| No           |           | 178| 74.2  | 117| 84.2  | 29 | 50.0  | 24.9; p < 0.001 | 32 | 74.4 |
| Yes          |           | 62 | 25.8  | 22 | 15.8  | 29 | 50.0  | 11          | 25.6 |
| Behavioral change |     | 123| 51.3  | 58 | 41.7  | 44 | 75.9  | 19.1; p < 0.001 | 21 | 48.8 |
| No           |           | 117| 48.8  | 81 | 58.3  | 14 | 24.1  | 22          |     |
| Yes          |           | 178| 74.2  | 117| 84.2  | 29 | 50.0  | 24.9; p < 0.001 | 32 | 74.4 |
| Cognitive decline |     | 212| 88.3  | 138| 99.3  | 51 | 87.9  | 13.5; p = 0.0002 | 23 | 53.5 |
| No           |           | 28 | 11.7  | 1  | 0.7   | 7  | 12.1  | 20          | 46.5 |
| Yes          |           | 212| 88.3  | 136| 97.8  | 41 | 70.7  | 33.1; p < 0.0001 | 35 | 81.4 |
| Frontal lobe disorder |     | 28 | 11.7  | 3  | 2.2   | 17 | 29.3  | 8           | 18.6 |
| No           |           | 196| 81.7  | 124| 89.2  | 37 | 63.8  | 17.7; p < 0.0001 | 35 | 81.4 |
| Yes          |           | 44 | 18.3  | 15 | 10.8  | 21 | 36.2  | 8           | 18.6 |
| Linguistic presentation |     | 231| 96.3  | 130| 93.5  | 58 | 100.0 | p = 0.06* | 43 | 100.0 |
| No           |           | 9  | 3.8   | 9  | 6.5   | 0  | 0.0   | 0           | 0.0 |
| Yes          |           | 230| 95.8  | 131| 94.2  | 58 | 100.0 | p = 0.11* | 41 | 95.3 |
| Progressive apraxia |     | 10 | 4.2   | 8  | 5.8   | 0  | 0.0   | 2           | 4.7 |
| No           |           | 233| 97.1  | 134| 96.4  | 57 | 98.3  | p = 0.67* | 42 | 97.7 |
| Yes          |           | 7  | 2.9   | 5  | 3.6   | 1  | 1.7   | 1           | 2.3 |
| Hyperemotionality |     | 227| 94.6  | 133| 95.7  | 56 | 96.6  | p = 1.0* | 38 | 88.4 |
| No           |           | 13 | 5.4   | 6  | 4.3   | 2  | 3.4   | 5           | 11.6 |

*S Fisher exact test applied.

SPECT imaging was abnormal in 95% of subjects with the parietal region showing most hypoperfusion, followed by the temporal area, then frontal.

The neurological examination was normal in most (70%): evidence of apraxia, extrapyramidal dysfunction, frontal lobe abnormalities, linguistic anomalies and visuo-spatial problems were identified in the minority. In 35% of subjects with YOAD there was either low Aβ₁₋₄₂ or elevated total or phosphorylated tau.

Prodromal AD was seen in two patients.

**Frontotemporal dementia (FTD)**

There were 58 subjects with FTD. The majority were male. About 40% had more than 13 years
## Table 2

| Comorbidities | Disease Type | N   | Col % | N   | Col % | N   | Col % | χ² and p | N   | Col % |
|---------------|--------------|-----|-------|-----|-------|-----|-------|----------|-----|-------|
| Age of onset (mean, SD) | EOAD | 56.6 | 5.6 | 56.5 | 5.45 | 57.1 | 5.66 | t = -0.67; p = 0.5 | 43 |
| Dyslipidemia | | No | 187 | 77.9 | 101 | 72.7 | 53 | 91.4 | 8.4; p = 0.004 | 33 | 76.7 |
| | | Yes | 53 | 22.1 | 38 | 27.3 | 5 | 8.6 | 10 | 23.3 |
| Hypertension | | No | 182 | 75.8 | 108 | 77.7 | 43 | 74.1 | 0.29; p = 0.59 | 31 | 72.1 |
| | | Yes | 58 | 24.2 | 31 | 22.3 | 15 | 25.9 | 12 | 27.9 |
| Alcoholism | | No | 218 | 90.8 | 128 | 92.1 | 52 | 89.7 | 0.31; p = 0.58 | 38 | 88.4 |
| | | Yes | 22 | 9.2 | 11 | 7.9 | 6 | 10.3 | 5 | 11.6 |
| Smoking | | No | 198 | 82.5 | 112 | 80.6 | 52 | 89.7 | 2.4; p = 0.12 | 34 | 79.1 |
| | | Yes | 22 | 17.5 | 11 | 7.9 | 6 | 10.3 | 9 | 20.9 |
| Anxiety | | No | 214 | 89.2 | 120 | 86.3 | 52 | 89.7 | 0.41; p = 0.52 | 42 | 97.7 |
| | | Yes | 26 | 10.8 | 19 | 13.7 | 6 | 10.3 | 1 | 2.3 |
| Depression | | No | 148 | 61.7 | 89 | 64.0 | 31 | 53.4 | 1.92; p = 0.17 | 28 | 65.1 |
| | | Yes | 92 | 38.3 | 50 | 36.0 | 27 | 46.6 | 15 | 34.9 |
| Type 1 diabetes mellitus | | No | 235 | 97.9 | 138 | 99.3 | 57 | 98.3 | p = 0.50* | 40 | 93.0 |
| | | Yes | 5 | 2.1 | 1 | 0.7 | 1 | 1.7 | 3 | 7.0 |
| Type 2 diabetes mellitus | | No | 224 | 93.3 | 130 | 93.5 | 55 | 94.8 | p = 1.0* | 39 | 90.7 |
| | | Yes | 16 | 6.7 | 9 | 6.5 | 3 | 5.2 | 4 | 9.3 |
| Ischemic heart disease | | No | 139 | 100.0 | 58 | 100.0 | NA | 40 | 93.0 |
| | | Yes | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 7.0 |
| Sleep disorder | | No | 216 | 90 | 129 | 92.8 | 52 | 89.7 | 0.54; p = 0.46 | 35 | 81.4 |
| | | Yes | 24 | 10 | 10 | 7.2 | 6 | 10.3 | 8 | 18.6 |

Education, and a similar number had less than 10 years. Most were married and were not overweight. Approximately half of the FTD population presented with memory loss. Behavioral change at presentation was also found in about half. There was no report of cognitive decline at presentation by the majority (71%). Most did not have extrapyramidal dysfunction. A frontal lobe syndrome was seen in about 30% at presentation and linguistic presentation in 36%. Hyperemotionality and psychomotor slowing were uncommon. No patients had posterior cortical atrophy or progressive apraxia (Table 1). The mean age of onset was 57.1 years (1 SD = 5.66). Most did not have dyslipidemia, hypertension, or alcoholism, and about 90% were non-smokers. Furthermore, diabetes mellitus types 1 and 2, ischemia heart disease, and asthma were not strongly associated. Depression was observed in about half and most did not have anxiety (Table 2). There was minimal cancer and head injury (Table 3). The majority were right-handed. Half had a family history of dementia and about 26% had a first degree relative with dementia. Psychosocial stressors were identified in half. About 50% had died at the conclusion of the study, about 40% were at home and 10% were in a nursing home (Table 3).

The ACE-R and MMSE were mildly reduced at first assessment, and a year later; the ACE-R remained low. The TFC was slightly reduced at the initial and second assessments and more so thereafter (Table 5). The CBI and FRS showed scores that increased with time. Anxiety was identified in about 47% and depression in 10% (Table 2).

The EEG revealed epileptic activity in about 20% and slow wave changes in about 42% (Table 6). The MRI was abnormal in approximately 80%, showing atrophy; frontal and temporal atrophy were most prominent (Table 6). There was minimal amyloid binding (Table 6). The FDG PET scan was abnormal.
Table 3
Medical history

| Disease Type | Medical History | N  | Col % | N  | Col % | N  | Col % | χ² and p | N  | Col % |
|--------------|----------------|----|-------|----|-------|----|-------|----------|----|-------|
| Cancer       |                | 216| 90    | 124| 89.2  | 52 | 89.7  | 0.009; p = 0.93 | 40 | 93    |
|              |                | 24 | 10    | 15 | 10.8  | 6  | 10.3  | 3        | 7  |        |
| Head injury  |                | 205| 85.4  | 119| 86.5  | 49 | 84.5  | 0.04; p = 0.84 | 37 | 86    |
|              |                | 35 | 14.6  | 20 | 14.4  | 9  | 15.5  | 6        | 14 |        |
| Handed       | Ambidextrous   | 1  | 0.4   | 0  | 0.0   | 0  | 0.0   | 0.06; p = 0.81 | 1  | 2.3   |
|              | Left-handed    | 24 | 10    | 16 | 11.5  | 6  | 10.3  | 2        | 4.7 |       |
|              | Right-handed   | 215| 89.6  | 123| 88.5  | 52 | 89.7  | 40       | 93 |       |
| Family history | None          | 127| 52.9  | 78 | 56.1  | 29 | 50.0  | 4.67; p = 0.46 | 20 | 46.5  |
|              | Three 1° relatives or Two 1° relatives with other family | 8 | 3.3 | 2 | 1.4 | 4 | 6.9 | 2 | 4.7 |
|              | Two 1° relatives | 19| 7.9  | 13 | 9.4  | 5  | 8.6  | 1  | 2.3 |
|              | One 1° relatives with other family | 11| 4.6 | 7 | 5.0  | 2  | 3.4  | 2 | 4.7 |
|              | One 1° relatives | 56| 23.3 | 32 | 23.0 | 15 | 25.9 | 9 | 20.9 |
|              | Other family   | 19 | 7.9  | 7  | 5.0  | 3  | 5.2  | 9 | 20.9 |
| Psychosocial stressors | No significant stressors | 109| 45.4 | 57 | 41.0 | 29 | 50.0 | 1.35; p = 0.25 | 23 | 53.5 |
|              | Yes            | 131| 54.6 | 82 | 59.0 | 29 | 50.0 | 20 | 46.5 |
| Current status | Deceased      | 96 | 40    | 40 | 28.8 | 28 | 48.3 | 6.9; p = 0.03 | 28 | 65.1 |
|              | Nursing Home   | 32 | 13.3 | 21 | 15.1 | 6  | 10.3 | 5  | 11.6 |
|              | at Home        | 112| 46.7 | 78 | 56.1 | 24 | 41.4 | 10 | 23.3 |

Table 4
APOE genotyping

| APOE | N | % |
|------|---|---|
| ε2/ε3 | 11 | 8 |
| ε2/ε4 | 15 | 11 |
| ε3/ε3 | 49 | 35 |
| ε3/ε4 | 47 | 34 |
| ε4/ε4 | 15 | 11 |
| **N = 137; no result = 2** |

| APOE | N | % |
|------|---|---|
| ε2/ε3 | 6  | 10 |
| ε2/ε4 | 5  | 9  |
| ε3/ε3 | 21 | 37 |
| ε3/ε4 | 21 | 36 |
| ε4/ε4 | 4  | 8  |
| **N = 57; no result = 1** |

Other dementias

Uncommon causes of YOD included cerebral amyloid angiopathy \( (n = 3) \), LBD \( (n = 8) \), PSP \( (n = 9) \), and prion diseases \( (n = 3) \), among others. Most were male, had less than 12 years of education, were married, and were not overweight. Almost half presented with memory loss and cognitive decline, but most did not have behavioral change. Extrapyramidal dysfunction was seen in about half. The majority did not have a frontal lobe disorder, a linguistic presentation, progressive apraxia, hyperemotionality, or psychomotor. The mean age of onset was 56.4 ± 5.7 years.

Most did not have dyslipidemia, hypertension, or alcoholism. The majority did not smoke. Depression and anxiety were infrequent. Diabetes, ischemic heart disease, and sleep disorder were uncommon. Cancer and head injury did not occur much. Most were right-handed and about half had no family history. Approximately 50% had significant psychosocial stressors. About 65% had died and 12% were in a nursing home.

The ACE-R and MMSE were reduced, as was the TFC. The CBI and FRS showed abnormalities.

in most, 98% (Table 6). The frontal region was mostly involved but not other fields. The SPECT scan was abnormal in about 90%, especially in the frontal region.

The neurological examination was abnormal in 40%, showing frontal lobe phenomena, speech disturbance and extrapyramidal features (Table 7). 52% had one APOE ε4 allele (Table 4).
Table 5
Cognitive results

|                   | EOAD           | EoFTD          | Diff between EOAD and EoFTD | Other          |
|-------------------|----------------|----------------|-----------------------------|----------------|
|                   | n   | mean | std | median | n   | mean | std | median | Wilcoxon Two-Sample Test |
| MMSE              |     |      |     |        |     |      |     |        |                             |
| 1st               | 135 | 21.18| 6.28| 23     | 44  | 24.41| 5.24| 27     | p < 0.01                   |
| 2nd               | 111 | 20.22| 6.28| 22     | 24  | 22.63| 6.59| 24     | p < 0.05                   |
| 3rd               | 94  | 18.99| 6.58| 21     | 13  | 21.54| 5.39| 22     |                             |
| 4th               | 76  | 18.83| 6.32| 20     | 9   | 21.78| 6.38| 23     |                             |
| 5th               | 55  | 18.16| 6.02| 18     | 8   | 18.63| 8.50| 20.5   |                             |
| ACE               |     |      |     |        |     |      |     |        |                             |
| 1st               | 100 | 59.76| 19.82|64 | 30 | 69.82 | 20.02| 74 | p < 0.05 |
| 2nd               | 50  | 44.98| 23.59|48.5 | 18 | 64.44 | 21.14| 64 | p < 0.01 |
| 3rd               | 25  | 41.76| 22.73|43 | 11 | 59.09 | 19.19| 57 | p < 0.05 |
| 4th               | 11  | 33.91| 19.31|34 | 6  | 63.00 | 14.67| 57 | p < 0.01 |
| DASS_depression   |     |      |     |        |     |      |     |        |                             |
| 1st               | 80  | 8.28 | 9.22| 4      | 23 | 7.04 | 6.74| 6      |                             |
| 2nd               | 27  | 5.56 | 6.49| 4      | 6  | 7.50 | 9.50| 2.5    |                             |
| DASS_anxiety      |     |      |     |        |     |      |     |        |                             |
| 1st               | 80  | 7.64 | 8.74| 5      | 23 | 5.83 | 6.29| 5      |                             |
| 2nd               | 27  | 4.07 | 3.69| 3      | 6  | 14.33| 16.07|12     |                             |
| DASS_depression   |     |      |     |        |     |      |     |        |                             |
| 1st               | 80  | 10.06| 8.55| 8      | 23 | 11.13| 8.15| 10     |                             |
| 2nd               | 27  | 7.15 | 5.61| 7      | 6  | 13.67| 11.43|14     |                             |
| TFC               |     |      |     |        |     |      |     |        |                             |
| 1st               | 100 | 9.55 | 2.84| 10     | 25 | 10.96| 2.07| 12     | p < 0.05                   |
| 2nd               | 46  | 7.43 | 3.19| 7.5    | 10 | 10.65| 4.08| 11.5   | p < 0.05                   |
| 3rd               | 23  | 6.26 | 3.21| 6      | 2  | 6.50 | 2.12| 6.5    | p < 0.05                   |
| CBI_R             |     |      |     |        |     |      |     |        |                             |
| 1st               | 97  | 51.05| 32.23|44 | 27 | 51.19 | 30.68| 50 | 21 | 56.33 | 39.54 | 50 |
| 2nd               | 44  | 70.39| 37.49|70.5 | 10 | 57.40 | 33.18| 67.5 | 13 | 73.85 | 37.51 | 89 |
| 3rd               | 18  | 80.17| 36.98|76 | 4  | 60.00 | 33.83| 67.5 | 3  | 77.67 | 60.48 | 56 |
| FRS               |     |      |     |        |     |      |     |        |                             |
| 1st               | 99  | 49.62| 21.97|54 | 30 | 47.90 | 27.01| 46.5 | 22 | 49.64 | 30.05 | 53.5 |
| 2nd               | 44  | 34.50| 24.75|28.5 | 17 | 52.41 | 29.48| 53 | 13 | 27.92 | 20.05 | 20 |
| 3rd               | 20  | 29.20| 16.10|34 | 11 | 38.27 | 20.44| 37 | 2  | 29.50 | 37.48 | 29.5 |

The EEG was abnormal in about 80%, with epileptogenic changes in about 50%, with slow wave changes in the majority; the slow wave abnormalities consisting of both theta and delta frequencies.

The MRI was abnormal in roughly 70%, showing atrophy. Amyloid binding on PiB amyloid scanning was seen in almost 70% and the FDG PET scan was abnormal in most with predominantly frontal and parietal hypometabolism. The SPECT scan revealed comparable data. The neurological examination was abnormal in the majority. The CSF data was unhelpful. Nine patients had primary progressive aphasia and 3 with semantic dementia; their data is summarized in Table 7. Note that one of these patients diagnosed with primary progressive aphasia had AD at neuropathological assessment and the other frontotemporal lobar degeneration with tau proteinopathy compatible with corticobasal ganglionic degeneration.

Comparative data: EOAD and EoFTD

There were statistically more females than males in early onset AD (EOAD) than early onset FTD (EOFTD) (p = 0.001), whereas there were more males in EOFTD. People with EOFTD tended to be more overweight (p = 0.04). The EOAD population had statistically more memory loss and general cognitive decline (p < 0.001); there was statistically more behavioral change in EOFTD (p < 0.0001). EOFTD had extrapyramidal dysfunction (p = 0.0002) and more frontal lobe dysfunction (p < 0.0001).

There was no statistically significant difference in mean age of onset between EOAD and EOFTD.
Table 6
Physiological results

| Baseline physiological results | All   | EOAD | EOFTD | Diff btw EOAD and EOFTD | Other |
|--------------------------------|-------|------|-------|-------------------------|-------|
|                                | N Col % | N Col % | N Col % | χ² and p | N Col % |
| Total person (n)               | 240 139 | 58 26 | 43 20.8 | 0.0001 | 7 17.9 |
| EEG Normal                     | 58 25.8 | 25 18.4 | 26 52.0 | 1.0, p=0.32 | 21 53.8 |
| Abnormal (slow wave or epileptogenic) | 167 74.2 | 111 81.6 | 24 48.0 | 20.8, p<0.0001 | 7 17.9 |
| Missing                        | 15 3 | 8 4 |
| Epileptogenic                  | No | 164 72.9 | 102 75.0 | 41 82.0 | 1.0, p=0.32 | 21 53.8 |
| Yes                            | 61 27.1 | 34 25.0 | 9 18.0 | 18 46.2 |
| Slow wave                      | No | 66 29.3 | 27 19.9 | 29 58.0 | 25.3, p<0.0001 | 10 25.6 |
| Yes                            | 159 70.7 | 109 80.1 | 21 42.0 | 29 74.4 |
| Slow wave type                 | Delta | 24 15.6 | 18 17.0 | 21 14.2 | 1.6, p=0.46 | 4 13.3 |
| Theta                          | 58 37.7 | 37 34.9 | 9 50.0 | 12 40.0 |
| Theta and Delta                | 72 46.8 | 51 48.1 | 7 38.9 | 14 46.7 |
| Slow wave location_left        | No | 33 20.8 | 20 18.3 | 5 23.8 | 1.0, p=0.32 | 21 53.8 |
| Yes                            | 126 79.2 | 89 81.7 | 16 76.2 | 21 72.4 |
| Slow wave location_right       | No | 56 35.2 | 42 38.5 | 6 28.6 | 0.75, p=0.39 | 8 27.6 |
| Yes                            | 103 64.8 | 67 61.5 | 15 71.4 | 21 72.4 |
| Slow wave location generalised | No | 108 67.9 | 71 65.1 | 21 100.0 | 16 46.2 |
| Yes                            | 73 31.3 | 48 36.1 | 13 22.8 | 13 44.8 |
| MRI Normal                     | 73 31.3 | 48 36.1 | 13 22.8 | 13 44.8 |
| Abnormal                       | 160 68.7 | 85 63.9 | 44 77.2 | 31 72.1 |
| Missing                        | 7 6 | 1 0 |
| Frontal atrophy                | No | 193 82.8 | 118 88.7 | 40 70.2 | 9.6, p=0.002 | 35 81.4 |
| Yes                            | 40 17.2 | 15 11.3 | 17 29.8 | 8 18.6 |
| Global atrophy                 | No | 212 91.0 | 122 91.7 | 54 94.7 | 1.0, p=0.32 | 36 83.7 |
| Yes                            | 21 9.0 | 11 8.3 | 3 5.3 | 7 16.3 |
| Temporal atrophy               | No | 182 78.1 | 117 88.0 | 26 45.6 | 38.4, p<0.0001 | 39 90.7 |
| Yes                            | 51 21.9 | 16 12.0 | 31 54.4 | 4 9.3 |
| Parietal atrophy               | No | 209 89.7 | 116 87.2 | 52 91.2 | 0.63, p=0.43 | 41 95.3 |
| Yes                            | 24 10.3 | 17 12.8 | 5 8.8 | 2 4.7 |
| Mesial temporal atrophy        | No | 220 94.4 | 122 91.7 | 55 96.5 | 1.0, p=0.32 | 43 100.0 |
| Yes                            | 13 5.6 | 11 8.3 | 3 5.3 | 0 0.0 |
| Posterior cortical atrophy     | No | 231 94.4 | 131 98.5 | 57 100.0 | 1.0, p=0.32 | 43 100.0 |
| Yes                            | 2 0.9 | 2 1.5 | 0 0.0 | 0 0.0 |
| PET amyloid                    | Normal | 7 13.5 | 0 0.0 | 5 7.1 | 0.0001, p=0.74 | 2 33.3 |
| Abnormal (amyloid binding)     | 45 86.5 | 39 99.0 | 2 2.8 | 4 66.7 |
| FDG-PET                        | Normal | 4 2.0 | 2 1.6 | 1 2.3 | 1 3.1 |
| Abnormal (Gyri or hypometabolism) | 200 98.0 | 127 98.4 | 42 97.7 | 31 96.9 |
| Any Gyri                       | No | 2 1.0 | 1 0.8 | 0 0.0 | 0.0001, p=1.0* | 1 3.2 |
| Yes                            | 198 99.0 | 126 99.2 | 42 100.0 | 30 96.8 |
| Any hypometabolism             | No | 120 60.0 | 62 48.8 | 36 85.7 | 0.0001, p<0.0001 | 22 71.0 |
| Yes                            | 80 40.0 | 65 51.2 | 6 14.3 | 9 29.0 |
| Anterior cingulated Gyri       | No | 183 91.5 | 118 92.9 | 38 90.5 | 0.74, p=0.0001* | 27 87.1 |
| Yes                            | 17 8.5 | 9 7.1 | 4 9.5 | 4 12.9 |
| Post-cingulate Gyri            | No | 133 66.5 | 68 53.5 | 40 95.2 | 0.0001, p<0.0001 | 25 80.6 |
| Yes                            | 67 33.5 | 59 46.5 | 2 4.8 | 6 19.4 |
| Frontal hypometabolism         | No | 80 40.0 | 61 48.0 | 10 23.8 | 7.6, p=0.006 | 9 29.0 |
| Yes                            | 120 60.0 | 66 52.0 | 32 76.2 | 22 71.0 |
| Parietal hypometabolism        | No | 43 21.5 | 9 7.1 | 21 59.5 | 54.0, p<0.0001 | 9 29.0 |
| Yes                            | 157 78.5 | 118 92.9 | 17 40.5 | 22 71.0 |
| Precuneus hypometabolism       | No | 129 64.5 | 58 45.7 | 42 100.0 | 0.0001, p<0.0001 | 29 93.5 |
| Yes                            | 71 35.5 | 69 54.3 | 0 0.0 | 2 6.5 |
| Temporal hypometabolism        | No | 43 21.5 | 27 21.3 | 5 11.9 | 1.80, p=0.18 | 11 35.5 |
| Yes                            | 157 78.5 | 100 78.7 | 37 88.1 | 20 64.5 |
| Occipital hypometabolism       | No | 176 88.0 | 110 86.6 | 41 97.6 | 0.046, p<0.0001 | 25 80.6 |
| Yes                            | 24 12.0 | 17 13.4 | 1 2.4 | 6 19.4 |

(Continued)
Table 6  
(Continued)

| Baseline physiological results                             | All | N  | Col % | EOAD | N  | Col % | EOFTD | N  | Col % | Diff btw EOAD and EOFTD | Other |
|-------------------------------------------------------------|-----|----|-------|------|----|-------|-------|----|-------|------------------------|-------|
| Various combination of above                                |     |    |       |      |    |       |       |    |       |                         |       |
| No                                                          | 199 | 126 | 99.5  | 42   | 100.0 |       |       |    |       |                         | 31    |
| Yes                                                         | 1   | 0.5 | 1     | 0.8  | 0    |       |       |    |       |                         | 0     |
| SPECT                                                       |     |    |       |      |    |       |       |    |       |                         |       |
| Normal                                                      | 16  | 5   | 9.0   | 4.9  | 6   | 12.8  |       |    |       | 2.97, p = 0.08          | 5     |
| Abnormal (Any hypoperfusion or post-cingulate)             | 161 | 98  | 91.0  | 95.1 | 41  | 87.2  |       |    |       |                         | 22    |
| Frontal hypoperfusion                                       |     |    |       |      |    |       |       |    |       |                         |       |
| No                                                          | 96  | 62  | 54.2  | 60.2 | 20  | 42.6  |       |    |       | 4.05, p = 0.04          | 14    |
| Yes                                                         | 81  | 41  | 45.8  | 39.8 | 27  | 57.4  |       |    |       |                         | 13    |
| Occipital hypoperfusion                                     |     |    |       |      |    |       |       |    |       |                         |       |
| No                                                          | 145 | 79  | 81.9  | 76.7 | 42  | 89.4  |       |    |       | 3.3, p = 0.07           | 24    |
| Yes                                                         | 32  | 18  | 18.1  | 24.3 | 5   | 10.6  |       |    |       |                         | 3     |
| Parietal hypoperfusion                                      |     |    |       |      |    |       |       |    |       |                         |       |
| No                                                          | 46  | 12  | 26.0  | 17.7 | 25  | 35.3  |       |    |       | 30.0, p < 0.0001        | 9     |
| Yes                                                         | 131 | 91  | 74.0  | 98.3 | 22  | 46.8  |       |    |       |                         | 18    |
| Temporal hypoperfusion                                      |     |    |       |      |    |       |       |    |       |                         |       |
| No                                                          | 80  | 47  | 45.2  | 65.6 | 18  | 38.3  |       |    |       | 0.70, p = 0.40          | 15    |
| Yes                                                         | 97  | 56  | 54.8  | 44.4 | 29  | 61.7  |       |    |       |                         | 12    |
| Precuneus hypoperfusion                                     |     |    |       |      |    |       |       |    |       |                         |       |
| No                                                          | 157 | 84  | 88.7  | 81.6 | 47  | 100.0 |       |    |       | p = 0.0009*             | 26    |
| Yes                                                         | 20  | 18  | 11.3  | 18.4 | 0   | 0     |       |    |       |                         | 1     |
| Post-cingulate                                              |     |    |       |      |    |       |       |    |       |                         |       |
| No                                                          | 154 | 84  | 87.0  | 81.6 | 45  | 95.7  |       |    |       | p = 0.02*               | 25    |
| Yes                                                         | 23  | 13  | 13.0  | 18.4 | 2   | 4.3   |       |    |       |                         | 2     |
| Neurological exam                                           |     |    |       |      |    |       |       |    |       |                         |       |
| Normal                                                      | 137 | 90  | 59.6  | 68.7 | 34  | 59.6  |       |    |       | 1.45, p = 0.23          | 13    |
| Abnormal                                                    | 93  | 41  | 40.4  | 31.3 | 23  | 40.4  |       |    |       |                         | 29    |
| CSF                                                         |     |    |       |      |    |       |       |    |       |                         |       |
| Normal                                                      | 22  | 17  | 71.0  | 65.4 | 2   | 100.0 |       |    |       | 0.87, p = 0.35          | 3     |
| Abnormal(low Aβ 1–42, or increased P-tau or increased Tau)  | 9   | 9   | 29.0  | 34.6 | 0   | 0     |       |    |       |                         | 0     |

*p = 0.0001, *p = 0.01, **p = 0.001

Table 7  
Linguistic and other forms of frontotemporal dementia

| Clinical Syndrome               | Clinical Subtype | N Median age at onset [range] | Sex M | F | Neuropathology / comment |
|---------------------------------|-----------------|-------------------------------|-------|---|-------------------------|
| Primary Progressive Aphasia     | PNFA            | 9 57 [39–64]                  | 6     | 3 | Patient #129
• FTD with Tau proteinopathy
• Corticobasal ganglionic degeneration
| SD                             | 3 60 [54–64]    | 3 0                           | 1     | 1 | Selective atrophy - right anterior temporal region
• No neuropathy
| Primary Prosopagnosia           | 1 58            | 0 1                           |       |   |                         |

There was more dyslipidemia in the EOAD population (p = 0.004), but no significant differences in other risk factors like hypertension and diabetes. There were no differences in the frequencies of APOE alleles, cancer, and head injury. Handedness and family history were not different between the two groups. There were more deceased subjects in the EOFTD group than EOAD (p = 0.03).

At first clinic contact the MMSE and ACE-R were significantly lower in the YOAD group than those in the young onset FTD (YOFTD) group; similar differences occurred in the second year; the ACE-R remained significantly higher in the YOFTD than YOAD in the third and fourth years. There were no significant differences in measures of depression, anxiety, and stress over the first two years between the two populations. The TFC was significantly higher in the YOFTD group at two years. There were no significant changes in the CBI or the FRS between the two groups in the first and second years.

There was significantly greater generalized slow wave activity in YOAD than YOFTD (p < 0.0001).
Epileptogenic activity was found in 25% of YOAD and frontal and temporal atrophy were significantly more prominent in YOFTD ($p = 0.002$ and $p < 0.0001$ respectively).

The proportion of patients with abnormal amyloid PET binding was very much greater in YOAD than YOFTD ($p < 0.0001$). Any FDG-PET hypometabolic change was greatest in YOAD ($p < 0.0001$), especially the posterior cingulate gyrus ($p < 0.0001$), the parietal region ($p < 0.0001$), and the precuneus ($p < 0.0001$). More patients had frontal hypometabolism with YOFTD ($p = 0.006$). The SPECT scan showed greater frontal blood flow reduction in YOFTD and YOAD ($p = 0.04$).

The $APOE$ genotyping reveals no major differences between EOAD and FTD.

There were no significant differences in neurological examination or CSF investigations.

### Neuropathology

Table 8 shows the ten patients who had neuropathological examinations. Of note was a man aged 41 years at onset who died at age 60 with a parietal lobe syndrome who was shown to have multiple sclerosis. Patient #76 had a dementing illness without extrapyramidal phenomena and was shown to have LBD. Two patients were shown to have FTD + motor neuron disease (MND) and had a TAR DNA-binding protein-43 (TDP-43) proteinopathy—one of whom was an indigenous Australian (with a family history of FTD and MND) but within which no known mutations were identified. Another patient (#38) who developed a frontal lobe disorder complicated by psychosis and then MND was shown to have TDP43+, ubiquitin positive neuropathology and had C9orf72 mutation, plus SIGMAR-1 mutation with an extensive family history. AD and LBD were found co-existing in patient #28 who had the simultaneous onset of dementia and a Parkinsonian syndrome and was diagnosed with both in life using neurodiagnostic features and FDG-PET imaging. Corticobasal degeneration was discovered in patient #396 who presented with non-fluency of speech and then developed a frontal lobe syndrome and extrapyramidal phenomena with a progressive dementia. Cerebral atrophy with unexplained small vessel disease and multiple strokes was established in patient #400, who presented with a gait disturbance with dementia and was shown to have multiple lacunae on imaging; she did not have hypertension, diabetes, dyslipidemia, heart or Fabry’s disease, and she did not smoke. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia was unearthed in patient #217 who experienced a dementing illness complicated by dystonia, limb kinetic apraxia, and seizures. Her MRI revealed extensive white matter changes. Her sister had a similar illness, but CSF-1 receptor mutations were not found. Patient #401 evolved with memory loss into a dementing illness and was shown to have marked hippocampal atrophy with non-vasculitic autoimmune encephalitis. Table 8 reveals two patients with the clinical syndrome of primary progressive aphasia with clinical presentation and divergent pathology: CBD and AD.

### Atypical presentations

Patients with unusual clinical syndromes not compatible with the above classifications and without neuropathology are revealed in Table 9. A frontal lobe disorder with progressive dementia and MND was found. Two patients with CBD were seen—one with cognitive decline, extrapyramidal dysfunction and progressive apraxia; the other with speech non-fluency and progressive apraxia. Patient #234 developed PD and after 5 years dementia, considered AD but LBD could not be excluded. A 59-year-old professional soccer player, known for his exceptional heading skills, emerged with dementia five years after an extrapyramidal syndrome and, relying on FDG-PET imaging, was diagnosed with LBD and AD (#293). Patient #363 presented with hemidystonia and progressed to a frontal lobe syndrome with vertical eye movement abnormalities and was considered to have a tauopathy in the PSP-FTD spectrum; despite the significant family history no tau or other mutations were identified. Progressive speech apraxia was found in a 55-year-old female who did not develop clinical or imaging evidence to suggest primary progressive aphasia. Multiple system atrophy of cerebellar type was diagnosed after a 58-year-old female presented with dysarthria.

Table 7 shows other forms of FTD including one patient with selective right anterior temporal atrophy presenting as primary prosopagnosia. Table 10 reveals our experience with non-amnestic forms of YOAD with posterior cortical atrophy syndrome being the most common.

Table 11 discloses the mutations identified in our YOAD and YOFTD populations: 3/139 YOAD group (2.2%) and 7/58 YOFTD group (12.1%). One patient was shown to have a prion mutation after a dementing illness with ataxia of 9 years’ duration [42].
| Patient No. | Sex | Age at onset | Clinical diagnosis before death | Age at death | Neuropathology diagnosis | Comments |
|------------|-----|--------------|---------------------------------|-------------|--------------------------|----------|
| 251        | M   | 41           | ● Behavioral                     | 60          | ● Dementia and frontal lobe syndrome in multiple sclerosis |          |
|            |     |              | ● Cognitive                      |             |                          |          |
|            |     |              | ● Frontal lobe syndrome          |             |                          |          |
|            |     |              | ● Memory loss                    |             |                          |          |
|            |     |              | ● bvFTD                          |             |                          |          |
| 76         | M   | 64           | ● Cognitive decline              | 67          | ● Lewy body disease      |          |
|            |     |              | ● Behavioral                     |             |                          |          |
|            |     |              | ● Memory loss                    |             |                          |          |
|            |     |              | ● Vascular cognitive impairment  |             |                          |          |
| 57         | M   | 57           | ● Behavioral & linguistic syndrome| 58          | ● FTLD + TDP 43 proteinopathy | FH–      |
|            |     |              | ● FTD                           |             | ● FTLD + MND (ALS)       |          |
|            |     |              | ● MND                           |             | ● Cerebral atrophy (Pathological subtype 2) |          |
| 261        | F   | 44           | ● Linguistic & behavioral syndrome| 48          | ● Cerebral atrophy       | Uncle MND + FTD |
|            |     |              | ● EOAD                          |             | ● FTD + MND              | Mother FTD |
|            |     |              | ● MND                           |             | ● TDP 43 proteinopathy   | Grandmother FTD |
| 217        | F   | 61           | ● Memory loss                    | 67          | ● Adult-onset leukoencephalopathy with axonal spheroids & pigmented glia (ALSP) | Sister – identical clinical picture |
|            |     |              | ● White matter disease           |             |                          |          |
|            |     |              | ● Dystonia                       |             |                          |          |
|            |     |              | ● Limb kinetic apraxia           |             |                          |          |
|            |     |              | ● Seizures                       |             |                          |          |
| 38         | M   | 56           | ● Behavioral                     | 63          | ● FTLD + MND             | Extensive FH |
|            |     |              | ● Cognitive decline              |             | ● UBQ+                   | Psychosis FTD |
|            |     |              | ● Frontal lobe disorder          |             | ● Ammon’s horn/Ant horn cells | MND |
|            |     |              | ● FTD                           |             | ● TDP+                   | C9orf72 mutation + Sigmar 1 |
| 28         | M   | 57           | ● Cognitive decline              | 73          | ● DLBD                   | ● Alzheimer pathology |
|            |     |              | ● Extrapyramidal disorder        |             | ● Atrophy frontal/temporal lobes |          |
|            |     |              | ● Memory loss                    |             | ● Pallor substantia nigra |          |
|            |     |              | ● Psychomotor slowing            |             | ● Corticobasal degeneration |          |
|            |     |              | ● EOAD                          |             |                          |          |
|            |     |              | ● Lewy body disease              |             |                          |          |
|            |     |              | ● Extrapyramidal syndrome        |             |                          |          |
|            |     |              | ● Frontal lobe syndrome          |             |                          |          |
|            |     |              | ● Linguistic difficulties        |             |                          |          |
|            |     |              | ● Memory loss                    |             |                          |          |
|            |     |              | ● CBS                            |             |                          |          |
| 396        | F   | 48           | ● Gait disturbance               | 52          | ● Atrophy frontal/temporal lobes |          |
|            |     |              | ● Arteriosclerotic               |             | ● Pallor substantia nigra |          |
|            |     |              | ● Encephalopathy                 |             | ● Corticobasal degeneration |          |
|            |     |              | ● Lacunes                        |             |                          |          |
| 400        | F   | 50           | ● Memory loss                    | 60          | ● Cerebral atrophy       | No cause identified |
|            |     |              | ● Small vessel disease –         |             | ● Small vessel disease – |          |
|            |     |              | ● leptomeningeal + parenchymal    |             | ● leptomeningeal + parenchymal |          |
|            |     |              | ● Multiple strokes – different size & shapes | | |          |
| 401        | M   | 50           | ● Memory loss                    | 54          | ● Hippocampal atrophy    |          |
|            |     |              | ● Non-vasculitic autoimmune      |             | ● Non-vasculitic autoimmune |          |
|            |     |              | ● Encephalitis with T-cell infiltrates |     | ● Encephalitis with T-cell infiltrates |          |

**DISCUSSION**

Our prospective studies of a community population of YOD patients confirm that AD and bvFTD are the most common types of YOD referred from the community to specialist neurology clinics devoted to their assessment. Subtypes of YOAD were uncommon like posterior cortical atrophy and linguistic presentations of AD. Progressive non-fluent aphasia, semantic dementia, and FTD-MND complex were uncommon in the FTD population. Other causes of YOD, such as cerebral amyloid angiopathy, LBD, and PSP, were unusual, as were prion diseases.

Women were more common in the YOAD group, supporting the contention that AD is more common in them, and adds weight to the notion that AD is more common in women in general [43]. Our findings support that this is not just a consequence of survival, as has been proposed in the elderly, but may reflect a biological predisposition in women in general; possibly
Table 9
Exceptional clinical syndromes without neuropathology

| Patient No. | Sex | Age at onset | Clinical Syndrome INITIAL | Clinical Diagnosis FINAL | Comments |
|-------------|-----|--------------|---------------------------|-------------------------|----------|
| 19          | M   | 55           | • Frontal lobe disorder   | • FTD                   | Died 2017 Mother – dementia (onset 40s) |
|             |     |              | • Cognitive decline       | • MND                   |          |
| 363         | M   | 54           | • Hemidystonia            | • Tauopathy             |          |
|             |     |              | • Altered gait            | • PSP-FTD spectrum      |          |
|             |     |              | • Personality change      | • Auditory hallucinations |          |
| 350         | F   | 55           | • Speech apraxia          | • Progressive speech apraxia | Died 2003 |
| 391         | M   | 63           | • Cognitive decline       | • Corticobasal syndrome |          |
|             |     |              | • Extrapyramidal dysfunction |                        |          |
|             |     |              | • Progressive apraxia     |                         |          |
| 397         | F   | 59           | • Non-fluency speech      | • Corticobasal syndrome |          |
|             |     |              | • Progressive Apraxia     |                         |          |
| 234         | F   | 57           | • Extrapyramidal dysfunction | • PD → EOAD              | Died 2014 Father+aunt – dementia |
|             |     |              | • Cognitive decline       |                         |          |
| 293         | M   | 59           | • Extrapyramidal dysfunction | • LBD not excluded      |          |
|             |     |              | • Memory loss             | • AD                    |          |
|             |     |              |                            |                         |          |
| 365         | F   | 58           | • Dysarthria              | • Multiple system atrophy |          |

Table 10
Non-amnestic forms of young onset Alzheimer’s disease

| Clinical Syndrome | N | Median age at onset [range] | Sex (M:F) | Neuropathology |
|-------------------|---|-----------------------------|-----------|---------------|
| PCA               | 12| 56 [48–63]                  | 3:9       | NFT + NP of AD (N = 2) |
| Logopenic         | 2 | 58, 61                      | 1:1       |               |
| Frontal           | 3 | 57, 59, 60                  | 2:1       |               |
| Dyscalculic       | 1 | 57                         | 0:1       |               |

related to the effects of estrogens and progestogens on the brain not contaminated by effects of aging, cerebrovascular disease, and cerebrovascular risk factors [44, 45].

There were more overweight people in FTD, probably because of the failure to suppress appetite and control satiety [46], possibly through a mechanism involving degeneration and dysregulation within the posterior hypothalamus and modulations of the Agouti-related polypeptide [47].

The involvement of the mesial temporal structures explains the greater association of memory loss in YOAD, along with cognitive decline [48] in comparison to YOFTD.

Interestingly dyslipidemia was the only cerebrovascular risk factor having some association with YOAD and in line with our other studies that did not identify cerebrovascular risk factors as being strongly associated with YOAD or YOD in general [11, 49]. However, the findings in this enquiry support the notion that dyslipidemia may contribute to the pathophysiology of young onset AD but not FTD possibly through mechanisms involving proliferative-activated receptor alpha and fatty acid catabolism [50].

APOE ε4 genotyping was not associated with YOAD or YOFTD in this study, in which controversial results exist on the association of APOE and YOAD [13, 14, 51, 52]. The relatively high frequency of APOE4 alleles in our investigation might relate to small numbers of patients studied and represent a sampling phenomenon. Other research reveals that the ε4 allele of APOE might be an independent factor for neurodegenerative pathways through exosome pathway dysfunction [53].

More patients had died by the conclusion of the study with YOFTD than YOAD, consistent with our previous investigations, and of others that YOFTD has more aggressive natural history than YOAD [10, 13, 14, 54].

Differences in natural history are reflected in cognitive testing scores between EOFTD and YOAD where lower scores are found in the latter in the first two years, consistent with our other data of a more
Table 11

Observed mutations in young onset dementia

| Diagnosis                              | Sex | Age at onset | Presentation | Mutation                      | Comments                                                                 |
|----------------------------------------|-----|--------------|--------------|-------------------------------|--------------------------------------------------------------------------|
| Alzheimer’s disease                    | M   | 37           | Amnesia      | Presenilin 1 M233T            | A member of a previously published pedigree with AD and progressive spastic paraparesis [91] |
|                                        | M   | 45           | Amnesia      | Presenilin 1 Q222H            |                                                                           |
|                                        | M   | 47           | Progressive spastic paraparesis | Presenilin 1 Exon 9 c. 869-1 G＞A |                                                                           |
| Frontotemporal dementia                | F   | 43           | Frontal lobe syndrome (FLS) | PGRN Exon 8 T2727 fs          | Tetranucleotide deletion in coding region causing frameshift and premature translation termination → nonsense mediated RNA decay |
|                                        | M   | 48           | Memory loss  | PGRN p. R493X c. 1477 C＞T    |                                                                           |
|                                        | M   | 56           | Psychosis    | C9orf72 4G2C expansion = 2450 | Developed motor neuron disease (MND)                                     |
|                                        | F   | 62           | FLS          | SIGMAR1 c.672*26 C＞T         | T- No MND in proband and 3 affected family members                        |
|                                        | M   | 58           | FLS          | SIGMAR1 c.672*51 G＞T         | MND in brother                                                           |
|                                        | M   | 58           | FLS          | PGRN p. R493X c. 1477 C＞T    |                                                                           |
|                                        | M   | 51           | Non-fluency of speech | PGRN Exon 7 c. [708+1 G＞A] | Mother died in her early 60s from Pick’s disease                          |
| Gerstmann-Straussier-Scheinker disease | M   | 42           | Erratic behavior; driving errors; poor short-term memory; ataxia | PRNP G131V mutation          | No family history; died after 9 years; abundant prior protein immunopositive plaques in cerebellum. |

aggressive initial cognitive deterioration in YOAD [12].

The EEG was more abnormal in EOAD, probably reflecting differences in synaptic processing and the function of apical dendrites and their depolarization as disturbed by the proteins Aβ and tau [55]. Studies by others suggest these proteins disturb synaptic function and that some of the earliest pathophysiological change in AD may be chemical-electrophysiological with epileptic and slow wave changes and may be a potential biomarker [56–59]. Slow wave changes in AD have been shown to relate to the severity of the dementia and probably a consequence of reduced levels of acetylcholine, axonal degeneration, and neuronal loss [60].

Structural MRI changes were found in about 70% of both populations, with frontal and temporal atrophy being useful discriminators in YOFTD, but not helpful, other than excluding other pathologies, in YOAD. Other studies also show this contribution to the diagnostic work-up of MRI in YOD [61].

All the patients with YOAD had abnormal amyloid binding, supporting the fundamental role that this protein has in the pathophysiology of YOAD and not YOFTD, a finding supported by other observations [62]. Furthermore, the study of YOAD removes the contaminating factors of age, cerebrovascular pathology, and trauma as contributing to amyloid deposition of AD [63].

The FDG PET scan was also useful in detecting hypometabolism in YOAD, especially in the posterior cingulate gyrus, parietal region, and precuneus—all markers of the default mode network, the brain network important in AD [64]. As predicted, frontal hypometabolism was more obvious in YOFTD [65]. The SPECT scans showed similar findings [66].

The CSF findings of low Aβ1-42 or increased tau was useful in YOAD and a helpful biomarker that might be useful in patients where other tests are unhelpful [67].

The neurological and blood work did not distinguish the two populations [68, 69].

Clinical-pathological studies in ten patients revealed some important observations and emphasize the importance of ongoing neuropathological investigation. White matter diseases of the brain can develop a dementing syndrome, including a frontal-like syndrome in multiple sclerosis [70] and dementia complicated by dystonia and seizures in [71]. A dementing syndrome was found in a non-vasculitic encephalitis with T-cells and is similar to patients reported [72, 73]. Unexplained small vessel with
multiple strokes causing vascular cognitive impairment was found and is evidence of a growing number of patients in whom no cerebrovascular risk factor is identified [74]. Patients with FTD-MND were observed with TDP43+ as noted by others; one of our patients was an indigenous Australian with a significant family history of MND and FTD for which no genetic cause was identified, an observation not previously recorded. In our explorations of neurodegenerative disorders in Aboriginal Australians, we have discovered Huntington’s disease [75] and prion diseases [76]. In this family with FTD-MND, we did not identify mutations in MAPT, GRN, C9orf72, TARDBP, FUS, UBQLNZ, and VCP. Whole exome sequencing did not identify any clinically relevant sequence variations. LBD was found in a man that was demented but did not have extrapyramidal features, a well-recognized phenomena [77, 78].

LBD and AD co-existed, a phenomenon increasingly recognized in young and old onset dementia, suggesting that predisposing factors to neurodegenerative processes may be unitary involving single or multiple protein pathways: α-synuclein → LBD, binary → Aβ and tau (AD) or greater. Recent studies show that in older brains even four misfolded proteins may complicate cognitive deterioration [79], whereas our observations suggest that this might be generalizable even to younger people. CBD with 4R tau was seen in a woman who presented with non-fluency of speech and evolved into progressive frontal lobe syndrome and extrapyramidal syndrome, linguistic presentations are well recognized in CBD [80–82]. Our experience in patients with linguistic presentations emphasizes the importance of clinical-pathological correlation in their understanding, a finding emphasized by others [83].

Eight patients had singular clinical presentations that did not fall into the broad categories of YOD as described so far and permission was not granted for neuropathological examination (Table 9). FTD with MND, CBD, a tauopathy in the PSP-FTD spectrum, PD complicated by EOAD, LBD+AD, an α-synucleinopathy, and progressive speech apraxia was found. These patients highlight the variability in phenomenology and clinical spectrum of YOD, considered by others [7, 84]. These results reveal the diversity that must be considered and sought for in patients presenting with the suspicion of YOD [2].

The limitations of this study are the relatively small number of patients studied (N = 240). The findings need to be confirmed in a large dataset. Furthermore, the study deals with qualitative phenomenological data.

Our studies reveal that YOD is heterogeneous, mostly sporadic, and not generally genetic in etiology, as revealed by the low frequency of mutations in our population, confirming our previous observations [20], and those of others [85–88]. Recent studies confirm the clinical heterogeneity of YOAD [89, 90]. These findings indicate that YOD is in general a nongenetic distinct clinical syndrome with multiple causes, natural histories, and pathological substrates and provides evidence for their stochastic nature where an abnormal protein sequence, generated by chance or somatic mutation, results in abnormal protein folding in a particular part of the brain and, as a result of the molecules biophysical features and the intracellular microenvironment, creates synthetic effects for protein over production → aggregation of misfolded proteins → cell death → protein relocation to the extracellular environment → uptake by neighboring neurons → progression of disease through the neuronal network → progressive atrophy and death [21].

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

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