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Course and Causes of Suspected Dementia in Young Adults: A Longitudinal Study

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The authors performed a prospective, unbiased analysis of a cohort of young patients assessed consecutively with the question of dementia. The onset of patients' cognitive symptoms was prior to the age of 65 years. A study group of 226 patients was followed for a mean duration of 4.59 ± 2.23 years (1 SD; range, 0.04-7.86 years). The diagnoses were established using published diagnostic criteria. A diagnosis of dementia was made in 112 patients (49.56%). Psychiatric disease was the most common diagnosis in those who did not have dementia (24.3%) followed by frontotemporal lobar degeneration (19.0%), Alzheimer's disease (11.9%), patients with cognitive symptoms who obtained normal neuropsychometric profiles (10.6%), nonneurological disorders (eg, obstructive sleep apnea [8.4%]), neurological disorders (eg, Parkinson's disease [4.9%]), and mild cognitive impairment (4.9%). The frequencies of frontotemporal lobar degeneration and psychiatric disease were higher than Alzheimer's disease, unlike in older populations.

Keywords: young-onset dementia; causes; progress

Dementia in young adults has attracted little attention until recently and is probably underrecognized, poorly diagnosed, misunderstood, and inadequately managed with limited resources and services in most countries.[1] This growing area of clinical neuroscience promises insights into brain functioning (eg, speech, memory) and the role of genes in producing brain disease. In addition, genetic etiologies are more likely in young patients, as mutations in the amyloid precursor protein gene, presenilins 1 and 2, and prion genes give rise to early-onset dementia.[2,3] Interest in dementia in young adults helps in the application of new genetic information in the diagnosis of dementia in young adults.[4,5] Expertise in the analysis of dementia in young adults is also important to detect new forms of dementia, such as new variant Creutzfeldt-Jakob disease (nvCJD).[6,7] This field of research is necessary to assist in the development of guidelines for the diagnosis and management of dementia in young adults, to aid in the provision of suitable services, and to act as a foundation for research. Here, we report our experience in identifying the causes of dementia in young adults.

The study of young-onset dementia has been advanced by Harvey et al,[8,9] who investigated its epidemiology and clinical symptoms. The studies of Feran et al[10] and Ratnavalli et al[11] highlight the clinical characteristics and the importance of frontotemporal lobar degeneration as a cause of dementia in young adults. A textbook devoted to the subject outlines the complexities surrounding young-onset dementia.[1] The subject of young-onset dementia has also been reviewed, in which the importance of accurate diagnosis to investigate treatable causes was highlighted.[12] The study of McMurtray et al[13] to determine the relative frequencies and characteristics of dementia between early-onset and late-onset patients discovered a significant number of patients with head trauma, alcohol abuse, and HIV infections as a cause of young-onset dementia.

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Materials and Methods

In 1996, a multidisciplinary clinic was established at the Neurosciences Unit in Perth, Western Australia, to investigate and manage young patients referred with suspected dementia. Patients were assessed consecutively, prospectively, and without selection bias. Clinic staff included neuropsychologists, psychologists, speech therapists, social workers, support staff, and research assistants, as well as a neurologist, psychiatrist, and geneticist. Patients were referred from external sources, and entry into the clinic was based on the onset of cognitive symptoms before the age of 65 years if the referring agency suspected dementia. All patients were externally referred from the community. Psychiatric referral accounted for 45% of patients, neurology referral 35%, general physicians 10%, general practitioners 8%, and 2% of patients were referred by self or family.

For the purposes of this study, dementia was defined as a deterioration in cognitive abilities that impairs the function of the patient. Because the focus was on young adults, only individuals in whom onset of cognitive symptoms occurred prior to the age of 65 years were included. Patients with Huntington's disease were excluded from this study; these patients are managed in a different clinic within the Neurosciences Unit and were not referred to the young-onset dementia clinic for assessment. Data from all patients who met these inclusion and exclusion criteria are presented.

The patients received a clinical and neurological examination, during which a full history was obtained from patient, caregivers, spouse, and family. Blood investigations were performed including full blood count and erythrocyte sedimentation rate, urea, creatinine and electrolytes, liver function tests, glucose, calcium, vitamin B_{12}, red blood cell folate, treponemal serology, and thyroid function tests. Imaging investigations including high-resolution multiplanar computed tomography (CT) scanning or magnetic resonance scanning, single-positron emission computed tomography, and, more recently, positron emission tomography were conducted.

Neuropsychometry was also performed, confirming dementia and used along with general clinical assessments, spouse and caregiver reports, and reports from members of the team and supplemented by the Mini-Mental State Examination.

The neuropsychological assessment included measures presented in Table 1 for all clients. As superior tools (such as the Delis Kaplan Executive Function System) became available, they were also incorporated into the regular assessment.

Table 1. Neuropsychological Measures Administered With the Highest Frequency Within Neuropsychological Assessment for Each Patient

General intellectual functioning
WAIS-R or WAIS-III
Memory functioning
Rey-Osterrieth Complex Figure
Rey Auditory Verbal Learning Test
Speed of processing/attention
Symbol Digit Modalities Test
Trail-Making Test
Language
Controlled Oral Word Association Tests
Category Fluency Test
Boston Naming Test
Executive functions
Wisconsin Card Sorting Test
Delis Kaplan Executive Function System
Visuospatial functions
Block design
Rey-Osterrieth Complex Figure, copy trial
Clock drawing
Apraxia testing

WAIS-R = Wechsler Adult Intelligence Scale–R; WAIS-III = Wechsler Adult Intelligence Scale, third edition.

Apraxia testing included upper limb function, such as making a fist, salute, wave goodbye, scratch your head, snap your finger; facial assessment, such as move your tongue, close your eyes, whistle, sniff, blow out a match; instrumental, such as use a comb/brush, use a spoon to eat, use a hammer, use a key; and complex, such as pretend to drive a car, knock on a door, fold a paper, light a cigarette, and play the piano. These are performed on command, imitated, or with an object.

The patients' neurological assessment, investigations, and neuropsychological assessment were coordinated through the clinic. Linguistic assessment and treatment were performed by speech therapists. Social work staff provided advice and practical support to patients and their families, such as networking with community support agencies as appropriate. The patients were managed long term as part of a multidisciplinary team model, and regular team meetings were arranged to facilitate the caring network. For all patients, diagnoses were established through rigorous application of published diagnostic criteria (Table 2), as well as through the findings of initial and follow-up assessments, neuropsychological assessment, and neuroimaging results.

Table 2. Diagnostic Criteria

Frontotemporal lobar degeneration[14]
Alzheimer's disease[15]
Psychiatric[16]
Dementia with Lewy bodies[17]
Mild cognitive impairment[19]
Vascular dementia[18]

Vascular dementia was diagnosed using the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences diagnostic criteria for vascular dementia.[18] Alcohol-related dementia was diagnosed using criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition).[16] The diagnosis in each patient was made after consideration by the neurologist after discussion and consensus with the managing team.

Mild cognitive impairment refers to the amnesic form of mild cognitive impairment and not vascular dementia.[19] Other forms of dementia were excluded on neuroimaging, and in this investigation, mild cognitive impairment was thought to be a precursor for the development of Alzheimer's disease (AD). Prion diseases were confirmed neuropathologically.

All participants had the same investigations and the same follow-up at 3- to 6-month intervals, or sooner if necessary. All patients had multiple follow-up visits, and the diagnosis was reviewed at each clinical contact. Repeat investigations were performed including imaging, Mini-Mental State Examinations, and neuropsychometry to document the natural history. All patients were subject to the same diagnostic criteria and follow-up.

Data collected included primary and secondary diagnoses, presenting complaints, and a measure of natural history. This crude measure was based on overall patient functioning and investigations carried out through the unit and was made by the chief neurologist after discussion with spouse, caregivers, and team members. The natural history was also assessed using neuropsychometry and the Mini-Mental State Examination. Labels assigned were *stable*, *impaired*, *declined*, or *deceased*.

All participants gave informed consent. The study has the approval of the Graylands-Selby-Lemnos Health Care Complex Ethics Committee (of which the Neurosciences Unit is an administrative component).

Table 3. Frequencies of Primary Diagnoses in a Sample of Younger Adults Referred With Suspect Dementia

Diagnoses	%	Frequency		Family History, %
		Male	Female	
Psychiatric	24.3	23	32	—
Frontotemporal lobar degeneration	19.0	21	22	4.6
Alzheimer's disease	11.9	13	14	11.1
Normal	10.6	12	12	—
Nonneurological	8.4	12	7	—
Mild cognitive impairment	4.9	5	6	—
Neurological disorders	4.9	6	5	—
Vascular dementia	3.1	3	4	—
Alcohol	2.7	5	1	—
Multifactorial	2.7	4	2	—
Prion diseases	2.2	2	3	—
Head injury	1.8	4	0	—
Unspecified dementia	1.3	1	2	—
Family history	0.9	1	1	100
Posterior cortical atrophy syndrome	0.9	2	0	—
Diffuse Lewy body disease	0.4	1	0	—
Total	100.0	115	111	

Results

There were 254 patients assessed prospectively with suspected dementia, of which 28 were excluded because their age at symptom onset exceeded 65 years. There were 115 men and 111 women in the resultant sample (N = 226). The mean duration of follow-up was 4.59 ± 2.23 years (1 SD; range, 0.04-7.86 years). Dementia was diagnosed in 112 individuals (49.5%). Table 3 presents the final diagnoses. Some patients transformed from 1 diagnostic group to another. Three patients who had an initial suspicion of frontotemporal lobar degeneration (FTLD) were shown to have a psychiatric disorder, and 1 patient with a psychiatric disorder had FTLD. One patient with the initial suspicion of AD had a psychiatric condition. No patients with mild cognitive impairment have evolved into a dementia syndrome. Psychiatric disorders were the most common cause of suspect dementia in those who did not have dementia after comprehensive assessment. This was followed by FTLD and AD. One patient was found to have a presenilin 1 mutation (Q222H) as a cause of his early-onset AD. No mutations in the τ gene were observed in the FTLD group.[20] Within the FTLD group, 36 patients had the frontal variant of FTLD, 6 had primary progressive aphasia,

and 1 was diagnosed with semantic dementia. A substantial number of patients with the suspicion of dementia were found to be normal. Neurological disorders, nonneurological processes, mild cognitive impairment, and other causes were less frequent (Table 3). Table 4 shows the age at referral and the age at time of study, duration of follow-up, and death.

The most common psychiatric diagnosis was depression, followed by bipolar disease and anxiety (Table 5).

All patients had neuroimaging. All patients diagnosed with a psychiatric disorder had a normal CT or magnetic resonance image (MRI) with nonspecific findings on functional imaging. The entire group of patients with FTLD had frontal and/or temporal atrophy on CT or MRI with appropriate changes on functional imaging. All patients with AD had mesial temporal atrophy with or without hippocampal or generalized atrophy. Functional imaging in most patients showed biparietal hypoperfusion or hypometabolism, distinct from FTLD patients who had frontal and temporal abnormalities. Patients with mild cognitive impairment had normal imaging, as did the patients with a diagnosis of normality. Imaging in the other diagnostic categories showed extensive small vessel ischemic changes in the white matter in patients with vascular dementia occupying greater than 25% of the area of the white matter. Findings strongly suggestive of cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with multiple confluent white matter lesions of various sizes were found; dilatation of the ventricular system in hydrocephalus without an obstructive cause and findings typical of the other diagnoses such as posterior cortical atrophy and multiple strokes were observed. The imaging findings in the remaining other diagnoses were nonspecific.

Primary dementing diseases, other than FTLD and AD, made up a heterogeneous group, of which prion diseases, including sporadic and familial CJD and fatal familial insomnia, were the most common and included posterior cortical atrophy syndrome and diffuse Lewy body disease (Table 3). The patient with familial CJD had the codon 200 mutation, and the patient with fatal familial insomnia had the codon 178 mutation in the prion gene. One patient was found to have a novel mutation in the prion gene (G131V) leading to Gerstman-Straussler-Scheinker variant of prion disease.[21]

Neurological disorders causing dementia other than the primary dementias included Parkinson's disease, Down's syndrome, communicating hydrocephalus, CADASIL, and other disorders (Table 6). A previously unrecognized CADASIL mutation in the *Notch* 3 was found (C260R).

Obstructive sleep apnea, proven by overnight polysomnography, was the most common cause of cognitive deficits in patients with nonneurological disease (Table 7). This was followed by other etiologies including hypoglycemic encephalopathy.

Memory loss, particularly short-term memory loss, was the most common symptom across all diagnostic groups. Memory loss was a concern reported by the patient. This was so even for patients with frontotemporal dementia. Those patients were seen early in their diagnosis. Memory loss is a report given by the patient in the early phase of his or her illness. A combination of symptoms such as memory loss and speech disturbance was the second most common group of presenting symptoms (Table 8).

Only 4.6% of patients with frontotemporal lobar degeneration and 11.1% of patients with AD had positive family histories for dementia. All other diagnostic categories had no family history (Table 3).

The natural history of the cohort was studied for a mean duration of 4.59 ± 2.23 years (1 SD; range, 0.04-7.86 years) across all diagnostic groups. Using an overall assessment of patient functioning (Table 9) and confirmed by their scores on the Mini-Mental State Examination (Table 10), the researchers found that patients with a psychiatric diagnosis remained stable or improved in comparison with patients with neurodegenerative disorders, who tended to deteriorate.

There have been 15 deaths in the patient population. Permission for 6 autopsies was obtained, and the postmortem diagnoses of FTLD was confirmed in 4 patients and AD in 2 patients. Patients with nonneurological diagnoses remained relatively stable overall, as did patients with mild cognitive impairment (Tables 9 and 10).

Discussion

This prospective evaluation of suspect dementia in young adults revealed psychiatric disorders, FTLD, and AD as the most common diagnoses, with memory loss the most frequent presenting symptom. We observed a low frequency of behavioral disturbance despite the prevalence of FTLD in our population. This probably relates to the fact that individuals presented to our clinic at the early stages of the condition

Table 4. Subgroup Data on Age of Referral, Age at Time of Study, Duration of Follow-up, and Age at Death

Diagnosis	Minimum, y	Maximum, y	Mean, y	Standard Deviation
Psychiatric				
Age of referral	26.41	64.30	50.85	9.31
Age at time of study	29.99	68.60	53.74	9.51
Duration of follow-up	0.38	6.7	2.89	1.52
Age at death	—			
Frontotemporal lobar degeneration				
Age of referral	31.52	61.40	58.70	8.10
Age at time of study	36.36	67.58	62.06	8.62
Duration of follow-up	0.50	4.98	3.39	1.29
Age at death	32.38	70.93	56.32	13.33
Normal				
Age of referral	29.10	64.20	51.22	9.75
Age at time of study	29.34	70.30	54.51	9.89
Duration of follow-up	0.24	5.30	3.30	1.30
Age at death	—			
Alzheimer's disease				
Age of referral	49.49	64.21	59.38	5.23
Age at time of study	53.17	71.79	62.73	5.53
Duration of follow-up	0.58	5.20	3.35	1.31
Age at death	60.69	71.29	67.36	5.80
Nonneurological				
Age of referral	23.55	64.74	51.97	10.57
Age at time of study	27.44	67.65	55.14	10.60
Duration of follow-up	0.11	5.15	3.17	1.58
Age at death	—			
Mild cognitive impairment				
Age of referral	41.62	64.36	56.00	7.87
Age at time of study	42.47	70.60	59.00	7.88
Duration of follow-up	0.86	5.15	3.80	1.42
Age at death	—			
Neurological disorders				
Age of referral	33.08	64.61	53.75	8.85
Age at time of study	35.49	68.99	57.00	9.07
Duration of follow-up	0.17	5.05	3.25	1.35
Age at death	43.30	43.30	43.30	
Vascular dementia				
Age of referral	54.81	64.90	60.63	4.38
Age at time of study	59.75	70.26	63.77	4.07
Duration of follow-up	0.20	4.94	3.14	1.40
Age at death	58.66	58.66	58.66	
Alcohol				
Age of referral	43.32	61.99	53.88	7.09
Age at time of study	48.24	65.72	57.75	6.40
Duration of follow-up	1.67	5.03	3.87	1.21
Age at death	—			
Multifactorial				
Age of referral	52.95	64.92	57.51	4.33
Age at time of study	54.54	65.51	59.97	3.89
Duration of follow-up	0.59	4.34	2.46	1.32
Age at death	—			
Head injury				
Age of referral	39.06	53.88	46.65	6.50
Age at time of study	42.52	58.97	49.43	7.34
Duration of follow-up	1.05	5.09	2.78	1.86
Age at death	—			

Table 4. (continued)

Diagnosis	Minimum, y	Maximum, y	Mean, y	Standard Deviation
Unspecified dementia				
Age of referral	51.73	51.73	51.73	
Age at time of study	52.83	52.83	52.83	
Duration of follow-up	1.10	1.10	1.10	
Age at death	—			
Family history				
Age of referral	33.45	43.11	38.28	6.83
Age at time of study	34.15	43.43	38.79	6.56
Duration of follow-up	0.32	0.70	0.51	0.27
Age at death	—			

Table 5. Psychiatric Diagnoses

Diagnosis	%	Frequency
Depression	72.7	40
Bipolar	7.3	5
Anxiety	5.5	2
Psychosocial stressors	3.6	1
Posttraumatic stress disorder	1.8	1
Attention deficit hyperactivity disorder	1.8	1
Unspecified	7.3	5

Table 6. Frequencies of Specific Diagnoses in the Patient Groups With Neurological Conditions (n = 12)

Diagnosis	%	Frequency
Parkinson's disease	27.3	3
Down's syndrome	18.2	2
Multiple system atrophy	9.1	1
Communicating hydrocephalus	9.1	1
Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy	9.1	1
Extrapyramidal syndrome	9.1	1
Multiple sclerosis	9.1	1
Stroke	9.1	1

Table 7. Nonneurological Diagnoses (n = 19)

Diagnosis	%	Frequency
Obstructive sleep apnea	63.16	12
Hypoglycemic encephalopathy	15.79	3
HIV encephalopathy	5.26	1
Pituitary surgery	5.26	1
Postcoronary artery bypass grafting	5.26	1
Carbon monoxide poisoning	5.26	1

Table 8. Frequency of Presenting Symptoms Across All Diagnostic Categories (n = 16 Diagnostic Categories)

Category	Frequency
Memory loss	12
Speech disturbance	4
Carer concern	4
Behavioral disturbance	4
Positive family history	4
Poor concentration	2
Combination	11

before prominent behavioral symptoms became manifest. In our experience, memory loss was the most common presenting symptom in patients with FTLD, with some patients having a combination of presenting symptoms including behavioral disorder. The frequency of psychiatric disorders in this sample may in part be reflective of our referral base and also due to the geographical location of the unit adjacent to the state's tertiary psychiatric referral center. However, previous studies have also found this pattern. For example, a study of early-onset dementia in Liverpool also found a high frequency of psychiatric disease.[10] No patients with the primary diagnosis of depression developed dementia over the duration of their follow-up in this study, in which the mean duration of follow-up was 4.82 years (range, 0.8-6.7 years) in the patients with depression.

Epidemiological studies in Britain have established that the prevalence of dementia in adults aged 30 to 64 years is approximately 54 per 100 000.[9] The prevalence rate for early-onset AD has been estimated at 35 per 100 000, similar to other European studies.[11,22-24] Such studies have shown that FTLD and

Table 9. Frequencies (%) of Natural History Across Major Diagnostic Groups

Diagnosis	Stable	Improved	Decline	Death
Psychiatric	52.7	41.8	5.5	0
Frontotemporal lobar degeneration	18.6	0	60.5	20.9
Alzheimer's disease	7.4	0	77.8	14.8
Nonneurological	83.3	11.1	5.6	0
Neurological disorders	40.0	5.0	50.0	5.0
Mild cognitive impairment	72.7	9.1	18.2	0
Vascular dementia	28.6	0	57.1	14.3
Alcohol	66.7	16.7	16.7	0
Multifactorial	33.3	16.7	50.0	0

Table 10. Mini-Mental State Examination Scores At Diagnosis and at Follow-up

	At Diagnosis		At Follow-up	
Diagnosis	Range	Median	Range	Median
Psychiatric	20-24	22	19-25	22
Frontotemporal lobar degeneration	18-24	21	0-20	10
Alzheimer's disease	9-22	15.5	0-15	7
Nonneurological	19-25	22	18-24	21
Neurological	0-24	12	0-15	7
Mild cognitive impairment	25-28	26.5	25-8	26.5
Vascular dementia	15-24	19.5	5-13	9
Alcohol	16-23	19.5	15-22	18.5
Multifactorial	14-24	19	7-20	13.5

AD were the most common diagnoses. While the sample on which the current results were based differed from these studies, our patients were not filtered to exclude psychiatric disorders. Our experience was similar in that FTLD and AD remained the most common neurodegenerative disorders in adults younger than 65 years.

A significant proportion of individuals with cognitive symptoms were normal on all tests. This is an important group and might be reflective of the entity of subjective memory impairment.[25,26] Patients with subjective memory impairment report problems with memory not confirmed by objective testing. Future research could follow this group long term to determine whether subjective memory loss in younger adults is a predictive factor in the subsequent development of dementia.

No patients with nvCJD were identified in this sample, which likely reflects the fact that this study was performed outside Europe, where this condition has been reported.[6,7] Prion diseases were found in 2.2% of our patient population.

It is of note that obstructive sleep apnea was the most common nonneurological diagnosis. This differential diagnosis should be investigated in patients with possible dementia, as it is a reversible cause of cognitive decline.[27] Previously published studies of cognitive decline in young adults have not emphasized the possibility of obstructive sleep apnea leading to suspect dementia.[28,29]

Diffuse Lewy body disease was not a common diagnosis in our population, being found in only 1 patient, contrary to findings from other studies.[9] This may be a result of the application of the fairly strict criteria to the diagnosis of dementia with Lewy bodies and referral bias.

The rates of vascular dementia in the elderly demented population tend to be higher than that in our patient population.[30-32] This probably relates to the younger age of our patient sample and the age-related basis of vascular disease.

The application of genetic information to our population has led to the discovery of a family with a presenilin 1 mutation, a new CADASIL mutation, a novel mutation associated with Gerstman-Straussler-Scheinker variant of prion disease, and families with familial CJD and fatal familial insomnia. This indicates that genetic studies in younger patients with dementia are likely to illuminate the role of genetic factors.[4,5]

Our findings highlight the multiple etiologies of dementia in young adults in an unbiased, prospective appraisal of a cohort of young adults. The results indicate the need for an intensive rigorous diagnostic workup including consideration of general medical conditions such as obstructive sleep apnea.

The finding of such a broad range of diagnoses and variable natural history supports the role of a multidisciplinary approach to research and understanding of cognitive decline in young adults. We believe our findings justify the need for specialized services. The natural history has helped clarify the etiology in those difficult patients in whom the diagnostic tests have yielded ambiguous results and reinforces the need for long-term follow-up. We have the concern that if young patients with the question of dementia are not approached using a comprehensive diagnostic and management strategy, then some

etiologies may be overlooked. Our findings support initiatives that more attention be directed to dementia in young adults.[33]

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