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Design of a Comprehensive Alzheimer's Disease Clinic and Research Center in Spain to Meet Critical Patient and Family Needs

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Abstract

Alzheimer' Disease (AD) affects people worldwide, and the prevalence is rising as the population ages. There is an international effort to understand the biology of AD in order to develop primary and secondary prevention strategies, and to develop effective therapeutic interventions for individuals who are already symptomatic. One of the critically important pieces of all national plans to address AD is the call for the development of service models for delivery of quality, effective care based on best evidence. We describe here one type of care model developed by the Fundació ACE, Institut Català de Neurociències Aplicades (Fundació ACE, Barcelona, Spain) that integrates diagnosis, therapy, follow-up care, day care and a day hospital, and does so in the context of an active clinical research and educational program. There were 13,048 individuals newly evaluated and diagnosed in *Fundació ACE* between 1996 and 2011. Of these, 6,132 had AD (47.0%), 3,871 mild cognitive impairment (MCI) (29.7%), and 1,958 had no cognitive impairment (15.0%). Follow-up information is available on 4,735 (47.3%) AD and MCI patients, and these indicate that MCI develops into dementia at a rate of 222.6/1,000 person years. APOE genotyping was available in 22.4% of the patients, and the $\epsilon 4$ allele occurred in 45.7% of the AD cases, 37.8% of the MCI, and 31.6% of those without cognitive impairment. *Fundació ACE* can serve as a model system that can be adapted to other settings within their specific cultural, governmental and legal constraints.

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Conflicts of Interest

The authors have no conflicts to declare.

Keywords

Dementia; Alzheimer's Disease; Spain; Natural History

Introduction

There were an estimated 36 million people worldwide living with dementia in 2010, primarily Alzheimer's Disease (AD) (1, 2). The number of cases, both in absolute and relative terms is expected to rise substantially as the population continues to age, in some cases tripling in the next 25 years (3). As a consequence, there is an increasing international effort to understand the biology of AD in order to develop primary and secondary prevention strategies, as well as to develop effective therapeutic interventions among individuals who are already symptomatic. In response to these needs, the United States government passed the National Alzheimer's Project Act (NAPA) on January 4, 2011 that requires the Secretary of the U.S. Department of Health and Human Services establish the National Alzheimer's Project to: create and maintain an integrated national plan to overcome AD; coordinate AD research and services across all federal agencies; accelerate the development of treatments that would prevent, halt, or reverse the course of AD; improve early diagnosis and coordination of care and treatment of AD; improve outcomes for ethnic and racial minority populations that are at higher risk for AD; and, to coordinate with international bodies to fight Alzheimer's globally.

At the same time as the U.S. Alzheimer's plan ("The Plan") was being developed, the Special Subcommittee on Aging of the United States Senate released its report comparing international approaches to AD and dementia (3). The subcommittee reached several conclusions based on their analysis. First, medical professionals "do not and cannot always properly diagnose" AD. Second, there is an international effort to develop of home and community-based services within existing healthcare delivery systems so that demented individuals can stay in their own homes for as long as possible. Third, as a consequence of this desire to preserve autonomy in demented individuals, the committee noted the challenge of providing coordinated and integrated care, particularly among those patients with a more severe form of dementia. Finally, the subcommittee examined the role of family members as the primary care providers to demented individuals. Thus, it is clear that there are both regional and international efforts to address the underlying causes of AD and dementia, its diagnosis, treatment, and the development of services and support mechanisms.

One of the critically important pieces of The Plan was the call for the development of service models, and to develop methods for delivery of high quality, effective care based on the best available evidence of efficacy. This is similar to what is already being done in other countries, and mirrors the call that was made by the Psychogeriatric Advisory Council to the Health Service of Catalonia (Spain)(Cognitive and Behavioral Disorders in Social Health Care) in 1998 to develop "concrete strategies and action[s] aimed at improving the diagnosis, evaluation and monitoring of the people affected" (pg. 101). Indeed, many countries in Europe now have national dementia strategies or are committed to developing

such strategies (4), and two of these (Britain, France) were part of the analysis made by the Senate Subcommittee on Aging.

There are a variety of model systems in place around the world that provide a range of care services, with each model reflecting the local cultural norms, as well as governmental and legal restrictions and expectations. A common thread in all of the discussions regarding research and services in AD and related dementias is the need for coordination of activities. Indeed, a coordinated site for providing clinical services in a patient – and family – centered environment, can provide the backbone onto which coordinated clinical and basic research can be placed. Fundació ACE, Institut Català de Neurociències Aplicades (Fundació ACE) has developed one type of integrated care model in Barcelona (Spain) that includes diagnosis, therapy, follow-up care, day care and a day hospital, and does so in the context of an active clinical research program. The Alzheimer's Education Center (ACE) was established in 1991, and has evolved based on the changing needs and demands of the patients and their families, and based on the changing evidence-based therapies and management techniques. While there are proposed *frameworks* for comprehensive clinical and research settings for AD and related dementias in the U.S. (5), we describe here the organization and inner workings of *Fundació ACE*, that has been in operation in Spain for more than 15 years.

Fundació ACE began the Memory Clinic in 1996 with the goal of addressing the growing demand for the treatment and education for those individuals who suffer from dementia, and to do so by offering personal attention to the patients and their families. What began solely as a Day Center, evolved to include the Memory Clinic that now has a new 10-year contract with the Health Ministry of the Government of Catalonia, guaranteeing the services of the clinic through 2022. In addition to providing services through the health system, *Fundació ACE* also provides care on a fee-for-service basis.

The Structure of Fundació ACE

Fundació ACE evolved an organizational structure that allows it to meet the needs of the patients, families, professionals and researchers, and to respond to changes in these needs over time. Details of the structure are presented in the supplemental material, but, briefly, the center is divided into five interacting groups that are managed by an *Administrative Team* that is responsible for financial oversight, communication among the other seven teams, and communications with external collaborators. The *Outreach Team* consists of a full-time coordinator as well as independent contractors who provide a comprehensive website, a monthly electronic magazine, and who manage teaching activities and international conferences. The *Memory Disorders Unit* is similar to the clinical core of many of the Alzheimer's Disease Research Centers in the US. It is structured as a referral center receiving patients from districts of greater Barcelona supported by the Health Ministry, as well as private patients. The unit includes neurologists, geriatricians, neuropsychologists, social workers, nurses and clinical and technical staff.

There is a *Continuity of Care Team Unit* that works with the patients through the therapeutic Day Center. The Center serves as an alternative to hospitalization or institutionalization; there is a daycare facility for people with late onset dementia, and a day hospital for people

with early onset dementia. The day care services group is designed to enhance, preserve, and promote the independence of the patient in their basic activities of daily living and to reduce caregiver burden. The team includes a Medical Director, an Assistant Manager, a Center Coordinator, Hospital Coordinator, Neurologists, a Geriatrician, Psychiatrists, Neuropsychologists, psychologists, social workers, nurses, clinical assistants, occupational therapists, physical therapists, and healthcare aides.

Finally, there is a team devoted specifically to *Research Brain Imaging*. This includes *brain imaging*, clinical and basic research, including genetics, bioinformatics, and Clinical Trials. The *Neuroimaging Group* manages the first line clinical neuroimaging modality (i.e., CAT scanning) as well as research-level imaging procedures that are parts of clinical trials and other funded research (e.g., MRI, SPECT, PET). A *Clinical Trials Team Unit* carries out studies funded by the pharmaceutical industry. The *Bioinformatics Group* includes *Data Management and Biostatistics Team* includes a data Managers and doctoral-level biostatisticians and physicists doctoral-level psychologist as well as information technology consultants who build and maintain the computer infrastructure for *Fundació ACE*, and who work to design experiments and analyze data from the researchers. Finally, there is *Basic Research Group* is focused on genetics *Team*. Fundació ACE has that laboratory facilities that process samples from all newly enrolled patients in order that the foundation to participate in genome wide association studies as well as other biomarkers studies.

All of the patients receive standardized neurobehavioral exams, including neuropsychological (6) and social work evaluations, as well as appropriate laboratory and neuroimaging studies. All diagnoses are assigned by the clinical team at a daily consensus conference. The diagnosis of AD is based on the NINCDS/ADRDA criteria (7), and standard research-level diagnostic criteria are used for classification of vascular dementia (8, 9), fronto-temporal dementia (10, 11), Lewy Body Dementia (12), Parkinson's Disease (13), and other relevant conditions affecting cognition in the elderly (e.g., depression using DSM-IV (14)).

Mild Cognitive Impairment (MCI) is classified in terms of amnesic and non-amnesic MCI by using the current criteria (15, 16) and requires the presence of measurable alterations in cognitive functions, not sufficient to warrant diagnosis of dementia. The patient (or their caregivers) must report alterations in memory and/or cognition, but there can be no declines in general intellectual abilities.

However, the diagnostic criteria for MCI within the Center changed over the past 15 years. Prior to 2006, patients who would have later met the criteria for MCI were classified as: Age-related cognitive impairment, age-related memory impairment, or Mild Cognitive Impairment (using the 1999 criteria (15)). From 2006 onward, the center used the current research criteria (16, 17) and added the additional qualifier of "Probable" (i.e., uncomplicated by concomitant medical conditions) and "Possible" (i.e., with an associated medical condition that could account for the impairment)(18). They were further differentiated by the presence or absence of a memory deficit.

Patients are referred to the Memory Clinic by their primary care physician, a consulting neurologist, or psychiatrist (for example). There is an initial interview by the social worker with the family (40 minutes) followed by an interview of the family by the neurologist (30 minutes) and a neurological examination of the patient (30 minutes). The neuropsychological evaluation (50 minutes) follows and the results are collated for presentation at the next day's consensus conference (approx. 10-15 minutes per patient). The final diagnosis using established research-level criteria (see above) is based on the results of the neurological, neuropsychological and social work valuations. A therapeutic plan is developed which can include pharmacological and nonpharmacological therapies, as well as access to social resources. A second appointment is scheduled at which time the family and patient are informed of the diagnosis and therapeutic options are discussed (30 minutes).

For follow-up visits a similar sequence is used, but the neurological exam is more focused (30 minutes) and the families spend the time with the social worker (30 minutes); the neuropsychological evaluation is repeated in its entirety (50 minutes). For those patients who are supported by the Catalan Health Service, funds are provided to support the three components of the visit. Among those patients whose dementia has progressed to a moderate-severe stage (i.e., CDR ≤ 2), the neuropsychological evaluation is replaced by a more extensive social work interview (i.e., ~80 minutes) in order to provide additional support to the patient and family. For private-pay patients (including those with private insurance policies), a similar plan is used (i.e., private pay does not result in additional attention or services).

The Growth of Fundació ACE

13,048 patients enrolled in the *Fundació ACE*, from 1996 through December 2011. The annual rate of examinations increased to 1,773 in 2011 from 390 in 1996; the cumulative number of all patients enrolled in the center is shown in Figure 1. Figure 2 shows the cumulative totals of the patients with AD and Mild Cognitive Impairment (MCI) groups.

Table 1 shows the basic characteristics of the patients broken down into summary diagnostic groups. A group of cognitively normal elderly subjects was recruited into a research project (19), and provides important comparative information. There are significant differences in age ($F(6, 11741) = 405.3$, $\xi^2 = .17$), Global Deterioration Scale (GDS) ($F(6, 6932) = 1661.5$, $\xi^2 = .59$) and Mini-Mental State Exam (MMS) score ($F(6, 6829) = 713.2$, $\xi^2 = .39$) such that the AD patients are older than the controls and the MCI patients, and had lower summary measures of mental status at study entry (Least Significant Difference (LSD) Tests, $p < .05$). Women were more common than men in all groups ($p < .05$). The patients without cognitive impairments were younger than those with cognitive disorders (LSD Test, $p < .05$). The characteristics of the MCI patients who entered after 2005 are shown in Table 2.

The number of follow-up visits has risen to 3,579 in 2011 (a total of 5,532 evaluations) from 256 in 1997 (65% of the new patients). The median number of years of follow-up for all patients through 2011, from entry until their last visit is 2.85 years (95% Confidence Interval = 2.78 – 2.92). Because the rate of enrollment is increasing, the median follow-up does not reflect the whole picture. For the patients enrolled in 2001, who had 10 years of possible follow-up, the mean time as a clinic patient is 6.98 (± 2.65) years. For those who enrolled in

2006, who have only five years of possible follow-up, the mean time as a clinic patient is 3.68 (1.89) years.

At least one follow-up visit was available on the 1396 patients who were initially classified with MCI after 2005. 73% of the Probable MCI patients developed AD during follow-up, and 51% of the Possible MCI patients developed dementia. Non-Amnesic MCI evolved into clinical dementia in 33% of the patients.

Discussion

Fundació ACE has provided diagnosis, management, day care, and day hospital facilities for the citizens in the catchment area around the city center of Barcelona since 1996. The primary diagnosis identified among the more than 13,000 patients was Probable AD, accounting for 47% of the patients with cognitive disorders. MCI accounted for a further 30% of individuals, and approximately 15% of all of the patients referred for evaluation were classified as having subjective complaints of cognitive impairment with no objective findings.

Fundació ACE can serve as a model system to be adapted to other settings within local cultural, governmental and legal constraints. Any new service models developed as a consequence of The Plan, for example, must be flexible enough to adapt to both short-term and long-term changes in the needs of the patients and families. One of the important differences between the plans outlined in the 1998 Catalan and the 2012 U.S. Plan documents was the relative emphasis on the families and on institutional care. Reliance on informal family caregivers likely reflects not only the (un)availability of a formal services, but also cultural norms (3). Thus, while the U.S. places greater emphasis on group or institutional care (while paradoxically not providing adequate funding), countries such as Spain rely more heavily on families to care for the ill and infirm. This is reflected in the organization and operation of *Fundació ACE*. In addition to Day Hospital services for individuals with memory complaints or mild dementia (which also serves as respite care for caregivers), *Fundació ACE* also offers educational services and specialized information to the families of the patients free of charge. The foundation's professional educational efforts focus on the geriatricians, neurologists, and psychiatrists who are the initial point of contact for the patients and families, and who make the initial referrals to the Memory Clinic, and who are responsible for many aspects of the general healthcare of the patients.

The integration of the diagnosis and management of patients with cognitive disorders is facilitated by the organization of the health care system in Spain. In order to be enrolled in a dementia clinic such as that at *Fundació ACE*, the patients must be referred by their primary care provider or a consulting physician, who are responsible for parts of the initial evaluation including laboratory studies and brain imaging. However, the neurological examination, psychiatric evaluation, social work assessment, and neuropsychological evaluation are all completed as part of the work of the Memory Clinic. The information from these specialty exams and the resulting diagnoses (with recommendations) are passed back to the primary physician, who is responsible for the total care of the patient's health. However, therapy (esp., pharmacotherapy) is the responsibility of *Fundació ACE*.

From a research perspective, the patients enrolled and followed in *Fundació ACE* provide a unique window into the characteristics of patients with dementia syndromes as they are typically seen in clinical care. Unlike research centers that focus on the identification of participants with few if any medical complications (since they are needed for pharmaceutical trials), *Fundació ACE* enrolls “all comers”. As such, the research team is in a position to confirm and extend findings from tertiary care research centers in a more clinically diverse population. Furthermore, as the number of *Fundació ACE* patients who are genotyped increases, it will be possible to examine the relative impact of various newly identified SNPs and their role in modifying risk for sporadic AD (20-29). Indeed, the patients from *Fundació ACE* serve as an excellent confirmation sample, as they have not provided their genetic material to other studies, and thus the data are entirely independent of other genome-wide association studies.

Fundació ACE provides a good, working model for integrated care in dementia. From the initial point of contact, patients and their families have a range of services that are offered to them by the Health Service through *Fundació ACE*, including pharmacological and non-pharmacological therapeutic interventions, day care, and a day hospital. The availability of patient-centered day services – especially those that provide respite for families and stimulation for patients – could potentially extend the period of higher quality of life, thus meeting one of the primary goals of the care of patients with AD and related dementias.

One of the principal differences between the care model implemented in *Fundació ACE*, and those used more commonly in the U.S. and other countries is the lack of a comprehensive approach to the care of the patients and their families in these other settings. As noted by the Subcommittee on Aging (3), care of demented patients tends to be fragmented, whereas in *Fundació ACE* care and management is more fully integrated. We are not aware of other clinics with this kind of integrated system that are generally open and available to all people in need, regardless of their ability to pay.

The World Health Organization has recommended that priority should be given to dementia research as a public health agenda (30), a call that is reminiscent of a proposal made in 2006 that, “Epidemiological surveillance is an essential instrument for planning, managing and distributing community health resources, for following up the natural history of chronic diseases and for assessing the impact of programmes of prevention” (31). *Fundació ACE* is able to integrate research into the context of providing care, not only by supporting intervention trials, but by the use of the patient database to provide insight into the natural and treated history of AD and related dementias. Lopez-Pousa and colleagues (31) outlined a simple, minimal (i.e., 36-item) dataset that could significantly advance our understanding of AD and related dementias, and this was shown to be a viable method for obtaining information about the prevalence and characteristics of dementia (32). This kind of data could then be used to study intra- and inter-regional trends, and might be of particular use in resource-limited areas. An effort such as this would require the cooperation of scores of facilities, and would require sufficient funding to support an independent data management and analysis system. But, there could be “a sequential implementation of the registry... so that it can be *adapted to each health district or region.*”(31)(italics added). Thus, as we have emphasized regarding the development of the *Fundació ACE* clinical services, such a

registry must be allowed to evolve, with the specific national, regional, and local variations to allow for the acquisition of the relevant data.

The goal of this report was to describe the workings of an existing AD care center that seems to meet many of the requirements specified by The Plan and by other international efforts to address AD and related dementias. What we cannot report is a cost:benefit analysis, or an econometric modeling of the services provided by *Fundació ACE*. Not only is that beyond our expertise and our available data, but the results likely would not generalize to other regions or countries with different health and social services, and different cultural expectations. However, we believe that *Fundació ACE* is able to deliver the services that are suggested by the various national plans, and does so in a cost-efficient manner.

The U.S. Plan acknowledges that, “Many nations have developed Alzheimer’s plans of their own that involve improved care and supports for people with Alzheimer’s disease and their caregivers, as well as enhanced research and public awareness. In implementing the actions in this plan, HHS and its federal partners will coordinate with global partners to enhance these plans, avoid duplication of effort, and optimize existing resources” (pg. 30); the experience of *Fundació ACE* has much to contribute these efforts. The *specific* methods and organization of *Fundació ACE* are likely not generalizable to all parts the world. But, the success of *Fundació ACE* shows that a model of integrated, patient-centered care with a built-in research emphasis, can be used elsewhere. Each center must evolve based on regional constraints, and on the needs of the patients, their families and the professionals who care for them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cumulative enrollment of all patients in *Fundació ACE* from 1996 through 2011.

Figure 2.

Cumulative enrollment of patients as a function of diagnostic groups. Probable AD is shown with a solid line (closed circles), Possible AD with a solid line (open circles), and all MCI patients with a dashed line.

Table 1
Characteristics of Fundacio ACE Participants

	Probable AD	Possible AD	Other Dementias	Mild Cognitive Impairment	Other Conditions	Subjective Complaints	Healthy Elderly
N	4530	517	1314	2028	1929	1218	73
Age	85.1 (7.8)	83.6 (7.7)	82.3 (9.0)	79.8 (8.9)	78.6 (11.9)	71.5 (12.1)	71.5 (8.4)
Education¹	26.8 (973)	37.8 (272)	40.0 (536)	43.8 (945)	39.8 (700)	57.9 (342)	67.1 (49)
Sex²	74.3 (3367)	74.1 (383)	60.7 (797)	66.3 (1345)	60.7 (1170)	65.0 (792)	60.3 (44)
APOE*4³	46.0 (645)	43.4 (86)	28.3 (75)	37.8 (253)	31.6 (74)	21.2 (18)	20.0 (12)
GDS	4.54 (.82)	4.60 (.80)	4.38 (.88)	2.97 (.22)	3.53 (1.1)	2.00 (.25)	1.27 (.48)
MMSE	17.4 (5.6)	18.3 (5.3)	20.4 (5.6)	25.3 (3.4)	23.0 (5.9)	28.6 (1.44)	29.6 (.79)

¹ Percent (N) with at least elementary school education. Total with education levels is 10,419.

² Percent (N) female

³ Percent (N) with at least one copy of the E*4 allele. Total number genotyped is 2,913

Table 2
Characteristics of Fundacio ACE MCI Participants After 2005

	Probable Amnesic MCI	Possible Amnesic MCI	Non-Amnesic MCI	Statistics ⁴
N	167	523	291	981
Age	77.4 (6.3)	75.5 (8.0)	75.4 (8.3)	4.89 (.02)
Education¹	46.4 (70)	40.7 (188)	52.1 (137)	8.91 (.10)
Sex²	62.9 (105)	70.2 (367)	64.6 (188)	4.41 (.07)
APOE*4³	52.3 (46)	36.7 (61)	18.5 (10)	16.4 (.23)
GDS	2.98 (.21)	2.96 (.26)	3.00 (.00)	0.46 (.00)
MMSE	24.7 (2.9)	25.0 (3.5)	26.3 (2.7)	17.1 (.48)

¹ Percent (N) with at least elementary school education. Total with education levels is 876.

² Percent (N) female

³ Percent (N) with at least one copy of the E*4 allele. Total with APOE genotyping is 308.

⁴ χ^2 or F (Phi or η^2)