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Young Onset Dementia study – A Prospective Cohort Study of Quality of Life and Specific Needs in Persons with Young Onset Dementia and their Families

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Abstract

Background: Young-Onset Dementia (YOD) causes challenges and concerns that are likely to affect quality of life and generate specific needs for health care, which may be different from what is observed in late onset dementia. The knowledge about the impact of YOD, in particular Fronto Temporal Dementia (FTD), on the affected families is scarce, and previous studies have underscored the importance of differentiating between diagnostic subgroups of YOD in future research. Accordingly, the aims of this study are to identify and compare factors influencing quality of life between persons with young onset FTD and Alzheimer's Dementia (AD) and their families as the condition progresses. An additional aim is to compare the use of health care services among younger and older persons with dementia, and to investigate the life-stage specific needs for health care services in persons with YOD.

Methods/Design: This is a two-year observational Nordic multicentre cohort study of community-dwelling persons with YOD and their families. Two diagnostic subgroups, each consisting of 75 dyads with AD and 75 dyads with FTD with symptom debut <65 years, will be included, and compared with a control group consisting of 100 older persons with dementia and onset >70 years. Participants are recruited from nine Nordic memory clinics.

Comprehensive assessments are made at baseline, 12 and 24 months, supplemented with telephone follow-ups at 6 and 18 months. Primary outcome measure is Quality of life measured by Quality of Life in Alzheimer's Disease (QoL-AD) and EuroQol-5D (EQ-5D). Secondary outcome measures are needs for health care services measured by Camberwell Assessment of Needs in the Elderly (CANE) and Resource Utilization in Dementia Lite (RUD Lite). The inclusion period is from February 2014 to February 2015, with follow-up data collection until February 2017.

Conclusion: The sample size, the outcome measures, and the explanatory factors chosen in this study will provide new knowledge of quality of life in families with young onset FTD and AD, and contribute to tailoring the health care services to the life stage-specific needs of families with YOD.

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Keywords: Dementia, Young onset dementia (YOD); Early onset dementia; Alzheimer's dementia; Frontotemporal dementia; Quality of life; Specific needs; Care needs; Resource utilization; Service provision; Family

Background

Dementia is a condition usually affecting older people, but dementia symptoms can also occur before the age of 65 years, defined as young or early onset dementia (YOD/EOD).The prevalence of dementia varies with age [1]. Estimates of the prevalence of YOD vary from 54 per 100000 in the age group 30-64 years in the UK to 260 cases of severe YOD per 100000 in the same age group in Finland [2,3].

Metabolic diseases and genetic causes due to inherited mutations play a more important role in YOD compared to dementia in older people [4]. Approximately 10% of YOD have been attributed to chronic alcohol abuse [5]. A recent Swedish study identifying risk factors in early adolescence for later development of YOD in men, raises concern for the contribution to YOD due to exposure to drugs and alcohol abuse in the younger population [6].

The diagnosis of YOD is difficult. The presenting symptoms in younger persons are often more heterogeneous than dementia in older persons [7,8]. Two of the most common types of YOD are Alzheimer's disease (AD) and Frontotemporal dementia (FTD), the latter becoming relatively more frequent in the youngest age cohorts, whilst AD is rare before the age of 40 [2]. The hallmark symptom in AD is memory impairment, while FTD is characterized by the "frontal syndrome" with

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changes in personality and behavior, and executive dysfunction, but with relatively intact memory in early stage. In some cases of FTD however, language deficits may be the only presenting symptoms of dementia. Hence, early symptoms of FTD may be atypical and easily misattributed to depression, stress or work situation, resulting in prolonged time from symptom debut to diagnosis [9-11]. In addition, the awareness about YOD in the general population and also in healthcare professionals is limited, and resources and facilities for dementia evaluation may vary between clinics, which may cause further diagnostic delay. Early diagnosis is especially important in eliminating underlying causes that might be treatable. Moreover, this period of uncertainty is a particularly difficult time for the families, stressing the need for early diagnosis and appropriate counseling.

There is no curative treatment available for YOD, but relief of behavioral and psychological symptoms in dementia (BPSD), an important strain on the families, may be provided [12]. Several autosomal dominant variants of both AD and in particular FTD have been identified, which is likewise an important issue in counseling families with YOD [4]. Recent studies on the longitudinal association between BPSD, unmet needs and the use of psychotropic medication in YOD emphasize the importance of identifying and addressing individual needs, and reducing the total load of psychotropic medication through multidisciplinary approach [13,14]. It is hard to predict progression of dementia in younger persons, as there is significant individual variation. Thus, there is a need for more information about the life-stage specific needs for younger persons with dementia during the progression of the disease [15,16]. Previous findings have underscored the importance of differentiating between the two diagnostic groups FTD and AD with regard to how the disease affects the quality of life in families with YOD [12].

The objectives of this study are to provide new knowledge of quality of life in younger persons with AD and FTD and their families as the condition progresses. Further, to describe their life stage-specific needs and experiences with the health care services, so as to tailor service provision and future health care planning.

Through longitudinal observation of the lives of persons diagnosed with YOD and their families, and a control group of older persons with dementia and their families over a period of two years, this study aims to confirm or reject the presented hypotheses: 1. Older persons with dementia and their families have a better preserved QoL than in YOD, 2. QoL in YOD is poorer among persons with FTD and their families compared to AD, 3. QoL deteriorates more in persons with FTD and their families after two years than in persons with AD and older persons with dementia and their respective families, 4. Families with YOD have life stage-specific needs thus generating specific needs for health care services, and 5. Families with YOD have unmet needs.

Methods

Design

This is a Nordic two-year multicenter, observational cohort study of community-dwelling persons with YOD and their families (Figure 1). Participants are recruited from nine Nordic memory clinics, listed in Appendix 1.

Study sample

150 dyads of persons with YOD and family members/significant others will be included, 75 with a diagnosis of AD and 75 with FTD. The inclusion criteria for the persons with YOD are debut of dementia symptoms before the age of 65, age at time of inclusion below 70 years, and community-dwelling, including assisted living facilities at the time

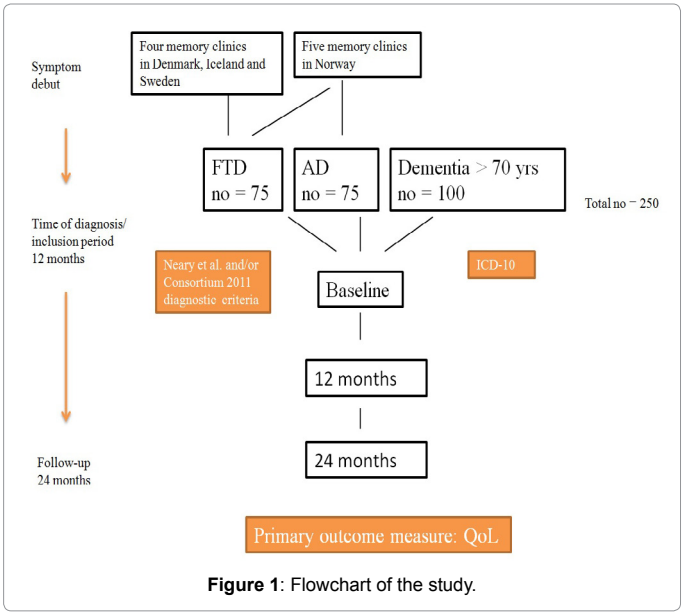

Figure 1: Flowchart of the study.

of inclusion. The diagnostic criteria are as described by Neary et al. (1998) and/or the International Behavioral Variant Frontotemporal Dementia Consortium criteria of 2011 for behavioral variant-FTD (bv-FTD), the Mesulam 2003 criteria for primary progressive aphasia, and the ICD-10 research criteria for AD [17,18]. There must be face-to-face contact at least once per week in the dyad. As controls we will include 100 dyads of older persons with a dementia diagnosis of AD, vascular dementia (VaD) or mixed AD/VaD according to the ICD-10 criteria, and their family members. The control group is recruited from a previous Norwegian study on the effect of psychosocial intervention on depression in persons with dementia and their family members [19,20].

The exclusion criteria are: Lack of informed consent; living in a nursing home or dementia-specific accommodation with staff 24/7; no appropriate family member/significant other; motor neuron disease (ALS) at the time of dementia diagnosis; other specific dementias with frontal dysfunction, such as Huntington's chorea, Down syndrome, HIV, or alcoholic dementia; mental retardation; current alcohol or substance abuse; need for interpreter in communication.

Data collection

Participants will be recruited from nine the memory clinics where they have been diagnosed according to clinical practice (appendix 1). In the Norwegian memory clinics the diagnostic work up is standardized by the Norwegian Dementia Registry diagnostic manual. An overview of the diagnostic workup in a Norwegian memory clinic is given by Brækhus et al. [21]. The Nordic counterparts are all members of the Nordic Network in Dementia Diagnostics (NIDD), an initiative of eight academic memory clinics in the Nordic countries and Lithuania, for comparison of diagnostic procedures and the promotion of common research projects. The diagnostic methods used in the memory clinics in this network were compared and turned out to be similar.

Screening of eligibility is based on the ICD-10 diagnosis classification and birth date from outpatient records. The families are contacted and informed either by the staff at the memory clinic or the project nurses. After receiving oral and written information, formal written consent is requested at the baseline registration. The assessments are mostly made at the memory clinics, but can in special circumstances be conducted at home visits.

The assessments of the person with YOD and the family member are conducted in parallel. In Norway the assessments are standardized by an outpatient team of two project nurses and a geriatrician conducting all study registrations.

The study combines the use of quantitative and qualitative methods for subgroups of YOD. The qualitative part of the study will include persons with YOD living alone, primary family members (spouses/cohabitants) of persons with young onset FTD, children from 17 to 30 years of age with a parent diagnosed with YOD, and family members of persons with YOD who have experiences with the Norwegian support contact service.

The one year inclusion period is from Feb 2014 to February 2015, with n=56 dyads included in Norway by November 2014.

Baseline information: Demographic variables, medical history, medication, diagnostic assessment including neuroimaging and biomarkers, and functional status are recorded, along with a comprehensive neuropsychological assessment for the person with YOD, Table 1. The family member provides proxy information and also information regarding their own health status, Table 2. Baseline information and outcome measures are already collected for the control group during a previous study [19,20].

Follow-up information: Each participant dyad is observed over a period of two years with semiannually follow ups. The same questionnaires and neuropsychiatric assessments are recorded at baseline, 12 and 24 months. In telephone interviews at 6 and 18 months we will record quality of life using the EQ-5D, any inter current events such as incident diseases, hospital admissions, changes in medication, changes in life situation, and level of care.

Outcome measures

The primary outcome measures are Quality of life measured by Quality of Life in Alzheimer's Disease (QoL-AD) and EuroQol-5D (EQ-5D). QoL-AD is a dementia specific and brief scale with good content, criterion and construct validity, and high inter rater reliability with all Cohen's kappa values >0.70 [21-23]. A good agreement is also shown with the EQ-5D [24,25]. QoL-AD consists of 13 items rated on a 4-point scale, with a score range from 13 to 52, a higher score indicating better QoL. It can be used as a self-rated instrument in mild to moderate and even severe, stages of AD [22]. In FTD, however, with early deficits in insight, this procedure could bias the results. Thus, in this study a proxy-rated version of QoL-AD is used as a supplement to EQ-5D for assessment of QoL in the persons with YOD. EQ-5D is a self-report questionnaire containing five descriptive items concerning mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In this study, the three level (EQ-5D-3L) score for no/moderate/severe problems is used. EQ-5D also contains a visual analog scale ranging from 0 to 100, 100 being the best imaginable health state and 0 the worst imaginable health state.

The secondary outcome measures are needs as measured by the Camberwell Assessment of Needs in the Elderly (CANE) and Resource Utilization in Dementia Lite (RUD Lite). CANE is a 24-item questionnaire covering possible problem areas in everyday life and psychosocial functioning with regard to informal and formal help, (un) met needs and satisfaction with the help received [26]. The help needed is scored on a scale from 1-3 from little to a lot of help, and the person with dementia and the family member rate these items separately. There are also two items for the needs of the family member concerning the psychological strain and the need for information.

RUD is the worldwide most commonly used questionnaire for

Measures and variables	Baseline, 12 and 24 months
Primary outcome measures Quality of life	Quality of Life in Alzheimer's disease (QoL-AD)* Euroqol-5D (EQ-5D)
Secondary outcome measures Needs	Camberwell Assessment of Need in the Elderly (CANE) Resource Utilization in Dementia Lite (RUD Lite) *
Explanatory variables Cognition Depression ADL Awareness Coping	Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE [29])*, Clinical Dementia Rating (CDR [30])*, Mini Mental Status Examination (MMSE [31]), clock drawing test [32], Consortium to Establish a Registry for Alzheimer's Disease (CERAD)-10 word list recall [33], CERAD -visuospatial figures [33], FAS [34] Trail making test-A/B [35], Boston Naming Test (BNT [36]), Montgomery-Åsberg Depression Rating Scale (MADRS [37]), Cornell Scale for Depression in Dementia (CSDD Cornell [38])*, NPI-Q* [39,40] I-ADL* [41] PSMS* [41] REED for asognosia [42] Locus of Control of Behavior (LoC) [43]

(*) by proxy
The persons with dementia in the control group have been assessed with QoL-AD (self- and proxy rated), NPI-Q, I-ADL and PSMS, and the Cornell Scale

Table 1: The scales used for assessment of the person with YOD.

Measures and variables	Baseline, 12 and 24 months
Primary outcome measures Quality of life	QoL-AD
Secondary outcome measures Needs	CANE item A and B
Explanatory variables Depression Relative's stress Coping	MADRS Geriatric Depression Scale (GDS) [44] Relative's stress scale (RSS) [45] LoC

The family members in the control group have been assessed with QoL-AD and GDS

Table 2: The scales used for assessment of the family member's own lived experience.

assessing the resource use in dementia care, allowing comparison across countries with different organization in health care provision, and recently updated in the 4.0 version [27,28]. In this study, RUD Lite is used as a supplement to CANE in assessing the needs for health care services.

For outcome measures and explanatory variables (Table 1 and Table 2).

Sample size and power calculation: Separate power calculations have been made for the persons with YOD and their families. The calculations are based on previous research measuring QoL using the QoL-AD instrument [19]. Among family members of younger and older persons with AD the mean score was 37.9 (SD 5.5) and 41.2 (SD 5.3), respectively, and among older persons with AD or VaD the value was 32.8 (SD 5.0, proxy rated) [19]. To our knowledge, no comparable values exist for FTD using the QoL-AD instrument. Our calculations are based on the assumptions that QoL is poorer among persons with FTD and their families compared to AD at baseline, with less worsening of QoL after two years in persons with AD and their families compared to FTD.

If the mean difference of the proxy rated score in the two YOD subgroups is 3.0 with SD 5.0 both at baseline and after two years, 44 persons with YOD are needed at 24 months follow-up in each group to detect a statistical difference at $p<0.05$ level, with 80% power.

Assuming a difference of 3.0 in mean QoL-AD score between the families of the two YOD subgroups and a SD of 5.6, 55 family members are needed at 24 month follow-up in each group to detect a statistically significant difference at $p<0.05$ level, with 80% power. Allowing for 20% drop-out during the two year follow-up, 75 YOD-dyads are required in each subgroup. For comparison between younger and older persons, we include data from 100 persons with onset of dementia above 70 years of age, making a total study population of 250 families with dementia.

Data analyses

The distribution of all variables will be compared between the two YOD subgroups, and between YOD and the control group. The distribution plots will be explored across the study groups and non-parametric or parametric tests will be used, as appropriate. Paired tests will be used to compare the outcome measures from baseline to follow up. A correlation matrix of all variables will be inspected to identify significant correlations, possible confounders and co-linearity between covariates. The relationships between the explanatory variables and outcome variables and variance explained by the study group affiliation will be analyzed by univariate and multivariate linear regression models. Goodness-of-fit of the models will be assessed by residual plots. Level of significance will be set to 5 %.

Qualitative methods will be used in four sub-studies for an in-depth understanding of subgroups of YOD. These interviews will assess their needs for services and support in order to reduce their burden associated with everyday life being a person with YOD or being a close family member. In addition, the family members' experiences of the Norwegian support contact service will be investigated.

Ethical considerations

The study has been approved by the Regional Committee for Medical and Health Research Ethics in Norway, the collaborating Nordic memory clinics applying to their respective National authorities.

Changes in the ability to give informed consent during the follow-up period constitute an important ethical consideration. Given previous consent to participation, continued consent is assumed as long as participants do not object to participation, and consent by proxy can be provided by the family member.

The study is registered in ClinicalTrials.gov (NCT02055092).

Discussion

Strengths

The results will provide important information about families with FTD, of which there is scarce knowledge concerning QoL and the impact on the whole family. This knowledge is essential in providing individualized and life stage-specific services to families with YOD, and to future planning of health care provision. A major strength of this study is the participation of memory clinics in different Nordic countries already collaborating inside the Nordic Network in Dementia Diagnostics. This allows for the inclusion of a large sample of persons with young onset FTD and their family members. To our knowledge, this study will be the largest longitudinal observational study of young onset FTD in Europe. This allows for robust statistical estimates.

The participating memory clinics have regional functions in diagnosing YOD. Our study population should therefore be representative for families with YOD in general, allowing for results to be applicable to the population for which it is intended. Moreover, the multinational dyad recruitment allows comparison across health care services with different organization and provisional systems, of importance in future planning of health care services tailored to individual needs for preservation of quality of life.

An additional strength is that all the Norwegian study registrations are made by the same outpatient team of a geriatrician and two experienced project nurses, familiar with the use of several of the questionnaires and trained in the use of the study-specific questionnaires. The study assessments are based on the Norwegian Dementia Registry's comprehensive diagnostic manual, using standardized and validated questionnaires/tests widely used in clinical and dementia research.

Furthermore, the long follow up period of two years should be sufficient to assess the main outcomes, and especially the impact on the family. The study also benefits from the combined use of quantitative and qualitative methods for an in-depth understanding of the situation of these families.

Limitations

The clinical dementia diagnosis is based on the ICD-10 classification. For research purposes we have supplemented the traditional diagnostic criteria of Neary et al. with the revised International Behavioral Variant Frontotemporal Dementia Consortium criteria of 2011 for bv-FTD [17,18]. The reason for this is increased sensitivity, perhaps at the expense of specificity, so as not to exclude persons who have been clinically diagnosed with FTD, but lacking perhaps one mandatory core criterion in early stage of the disease, i.e. early lack of insight or early emotional blunting. YOD composes a difficult diagnosis with an atypical presentation, and shifts in clinical diagnosis might also occur during a two-year follow-up at a memory clinic. However, assessment of the QoL and needs in families with YOD is likely to be beneficial to the families and provide important information regardless of diagnosis at 24 months.

One exclusion criterion is ongoing alcohol and substance misuse. In FTD excessive substance misuse may be the result of loss of inhibition, compulsive behavior and regulation of behavior as part of the frontal syndrome, and exclusion may lead to bias due to loss of an important

subpopulation of FTD, whose impact on the families is probably significant. Another selection bias is the dyads declining participation. They may constitute less resourceful families in need of support, whose experiences concerning unmet needs and quality of life would be of major importance significance. They may also be families who have had previous negative experiences with the health care services. Demographic data such as age and diagnosis is recorded for eligible candidates who decline participation.

Another weakness is that the study protocol has to be adapted to local variations, which constitutes a limitation due to country-specific variations in a questionnaire, i.e. MMSE. The protocol also comprises assessment scales not commonly used during ordinary diagnostic workup, i.e. CANE and RUD 4.0. These scales have been translated without the translated versions being validated, although the original questionnaires have been appropriately validated.

Furthermore, the stage of the disorder at time of inclusion ranges from newly diagnosed to advanced disease. This complicates the comparability between the AD and FTD groups, and also within groups. We believe the variance is balanced by the opportunity to assess a broad spectrum of YOD in life-stage specific circumstances different to older people with dementia, for whom the dementia-specific health care services are primarily intended. In addition to emphasizing the variety of life stage-specific needs, resourceful families with YOD may also help focusing on basic age-independent needs for peer involvement, active social participation and autonomy also in institutional care, beneficial to all affected by dementia at any stage in life.

Authors' contributions

The original study design was made by KE, PKH and AJ at the Norwegian Centre for Research, Education and Service Development. The study design as presented in this article has been outlined by the project group, consisting in addition of GS, HK, and LH. LH has written the protocol article, HK has assisted in writing it, and KE, GS, TBW, AJ, PH, JS and PKH have revised it in accordance with the JCTR guidelines.

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