Early and Late onset Depression in Late Life: a prospective study on clinical and structural brain characteristics and response to electroconvulsive therapy.

A. Dols* [a, b], F. Bouckaert* [c, d], P. Sienaert [d], D. Rhebergen [a, b], K. Vansteelandt [e, f], M. ten Kate [g], F-L. de Winter [c], H.C. Comijs [a, b], L. Emsell [c, h], M. Oudega [a, b], E. van Exel [a, b], S. Schouws [a, b], J. Obbels [d], M.P. Wattjes [g], F. Barkhof [g], P. Eikelenboom [a], M. Vandenbulcke [c] and M.L. Stek [a, b].

* Contributed equally and share first authorship

[a] Department of Old Age Psychiatry, GGZ inGeest/ VU University Medical Center, Amsterdam, the Netherlands

[b] EMGO+ Institute of Health and Care Research, VU University Medical Center, Amsterdam the Netherlands

[c] Old-age Psychiatry, KU Leuven, University Psychiatric Center KU Leuven, Leuven/Kortenberg, Belgium

[d] Academic Center for ECT and Neuromodulation, KU Leuven, University Psychiatric Center KU Leuven, Leuven/Kortenberg, Belgium

[e] Department of Psychiatry, KU Leuven, University Psychiatric Center KU Leuven, Leuven/Kortenberg, Belgium

[f] Research Group of Quantitative Psychology and Individual Differences, University Psychiatric Center KU Leuven, Leuven/Kortenberg, Belgium

[g] Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, the Netherlands

[h] Translational MRI, Department of Imaging and Pathology, KU Leuven & Radiology, University Hospitals Leuven, Leuven, Belgium

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Abstract

Objectives

The clinical profile of late life depression is frequently associated with cognitive impairment, aging-related brain changes and somatic comorbidity. This two-site naturalistic longitudinal study aimed to explore differences in clinical and brain characteristics and response to electroconvulsive therapy (ECT) in early (EOD) versus late onset (LOD) late life depression (respectively onset < and ≥ 55 years).

Methods

Between January 2011 and December 2013, 110 patients aged 55 years and older with ECT treated unipolar depression were included in Mood Disorders in Elderly treated with ECT study (MODECT). Clinical profile and somatic health were assessed. MRI scans were performed before the first ECT and visually rated.

Results

Response rate was 78.2%, and similar between the two sites, but significantly higher in LOD compared to EOD (86.9 vs. 67.3%, p=0.01). Clinical, somatic and brain characteristics were not different between EOD and LOD. Response to ECT was associated with late age at onset and presence of psychotic symptoms, and not with structural MRI characteristics. ~~There was a trend for medial temporal atrophy to be associated with higher odds for response in EOD, which was reversed in LOD.~~ In EOD only, the odds for a higher response were associated with a shorter index episode.

Conclusions

The clinical profile, somatic comorbidities and brain characteristics were similar in EOD and LOD. Nevertheless, patients with LOD showed a superior response to ECT compared to patients with EOD. Our results indicate that ECT is very effective in LLD, even in vascular burdened patients.

Background

The etiology and clinical presentations of late life depression (LLD) are rather heterogeneous compared to depression at a younger age. LLD is frequently associated with cognitive impairment, aging-related brain changes (e.g. mild cortical atrophy and vascular white matter changes) and somatic comorbidity (1-3). Within LLD, subsets can be defined by age at onset, with a variable cut off between studies ranging from 50 to 65 years (3). Early onset depression (EOD) is more often associated with a family history of affective disorders (4), anxiety features, and a more severe course of depression (3, 5). In contrast, late onset depression (LOD) is associated with somatic and neurodegenerative diseases (6) contributing to its onset and leading to a course with worse neurocognitive performance (7, 8), possibly as a prodrome of dementia (9). LOD is associated with a worse response to pharmacologic treatment as compared to EOD (3), possibly related to underlying cerebrovascular disease (10-12). In a comprehensive review on structural brain imaging and pharmacotherapy in LLD, poor outcome was most robustly linked with white matter integrity (13). In addition, vascular risk factors like hypertension, cerebrovascular disease, myocardial infarction and diabetes were specifically linked to LOD, so clinical profiling by age at onset may be a tool to direct treatment strategy. Nevertheless, differences between EOD and LOD may depend on the samples studied, as depressive symptomatology of melancholic inpatients with respect to EOD and LOD were found to be more alike than different (14, 15). Studies on treatment response in EOD and LOD combining vascular risk factors with imaging data on white matter integrity in well-defined samples are lacking to date.

In severe LLD, ECT is often the treatment of preference since it is more efficacious than pharmacotherapy (16, 17), even when other strategies have failed, with response rates of 60-70% (18, 19); moreover its side effects are milder than those associated with pharmacotherapy (20). In line with the better response rates for EOD treated with pharmacotherapy (11, 12), response to ECT may be better in EOD. Earlier studies by our group reported lower overall response rates to ECT in patients with medial temporal atrophy, but not white matter lesions, (21) and a faster response in patients with a smaller inferior frontal gyrus (22). However, these studies did not focus specifically on the possible role of age at disease onset.

Mood Disorders in Elderly treated with Electro Convulsive Therapy (MODECT), a two-site naturalistic, longitudinal study including older in-patients with severe unipolar depression treated with ECT was designed to study clinical characteristics and outcome of LLD treated with ECT.

The first aim of the present study was to describe the patients included in this cohort and to explore possible differences on demographical and clinical characteristics between the two inclusion sites. The second aim was to explore differences in clinical and structural brain characteristics between EOD versus LOD in a well-defined sample of LLD patients treated with

ECT and to identify predictors of response to ECT with regard to age of onset. We hypothesized that LOD would be associated with somatic burden, age-related brain characteristics and poorer response to ECT.

Methods

Sample

Data were obtained from the Mood Disorders in Elderly treated with ECT study (MODECT). Patients aged 55 years and older with severe unipolar depression according to Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria (23) referred for ECT were recruited from two tertiary psychiatric hospitals (GGZinGeest, Amsterdam, the Netherlands and University Psychiatric Center, KU Leuven, Belgium). Exclusion criteria were a DSM-IV diagnosis of bipolar disorder, schizoaffective disorder and a history of a major neurological illness (including Parkinson's disease, stroke and dementia). The diagnoses were made by a psychiatrist and confirmed by the Mini International Neuropsychiatric Interview (MINI) (24). Data collection started in January 1, 2011 and was finished in December 31, 2013. 110 patients were recruited: 67 in Amsterdam and 43 in Leuven (see figure 1).

Assessments

Demographic (age, sex, marital status, education) and clinical variables (duration of admission before ECT, number of previous episodes, number of admissions, duration of all admissions, duration of current episode) were obtained by interview and double-checked by chart review. Age at first depressive episode before 55 years was classified as early onset (EOD), a first episode at 55 years and older was defined as late onset (LOD), as in our previous cohort (21). Previous treatments for the current depressive episode were assessed with the Antidepressant Treatment History Form (ATHF) (25). Primary indication for ECT was indicated as pharmacotherapy resistance, life threatening symptoms, elective or other. The diagnosis of depression with or without psychotic symptoms was based on the DSM-IV criteria (MINI interview).

Physical comorbidity and medication use were assessed in a semi-structured interview inquiring about the presence of chronic obstructive pulmonary disease/ asthma/ emphysema, cardiovascular disease, myocardial infarction, hypertension, diabetes, cerebrovascular disease, arthrosis, (rheumatoid) arthritis, malignant neoplasms, migraine, thyroid disease, consequences of an accident (fractures, head injury or burns) permanent disability due to surgery (loss of a limb, ostomy), Parkinson's disease, other disease of the central nervous system, or other diseases. Smoking was categorized as never, ever or current. Alcohol use was measured by two questions based on the Alcohol Use Disorders Identification Test (AUDIT) (26) on frequency and amount of alcohol consumption.

The Montgomery Åsberg Depression Scale (MADRS) was used to evaluate the depressive symptom severity during the treatment course (27). In addition, we examined the patient's cognitive functioning by Mini-Mental State Examination (MMSE) (28). MADRS and MMSE

were collected by well-trained research nurses who were blinded to clinical information, including information on age at onset.

MRI Imaging

Whole-brain scans were obtained at baseline using a whole-brain 3T MRI system (General Electric Signa HDxt in Amsterdam, Philips Intera in Leuven) prior to ECT, one week after completion of ECT and six months after treatment. We acquired structural 3D T1-weighted images (MPRAGE) and axial fluid-attenuated inversion recovery (FLAIR).

At baseline, white matter hyperintensities (WMH) were rated on axial FLAIR images using the four-point Fazekas scale (29) and the Age-Related White Matter Changes scale (ARWMC) (30). The Fazekas scale is a whole brain scale ranging from 0 (no WMH) to 3 (large confluent areas of WMH). The ARWMC assesses WMH in 10 different brain regions, the score per region ranging from 0 to 3. Medial temporal lobe atrophy (MTA) was rated on the oblique coronal 3D T1 images using the 5-point Scheltens scale (31) ranging from 0-4. We calculated the mean of left- and right-hemispheric score. Scores of both sides were summed up and divided by two. Cortical atrophy was assessed on axial FLAIR images using the Pasquier 4-point global cortical atrophy (GCA) rating scale (32). Scores of left and right hemisphere were summed up and divided by two. Periventricular WMH were rated separately on a 3-point scale ranging from 0 (no periventricular WMH) to 2 (>5mm).

For the analysis, three groups were identified based on the MTA, Fazekas and GCA scores: 0 = no structural abnormalities, 1 = moderate structural abnormalities and ≥2 = severe structural abnormalities. The ARWMC scores of all regions were summed and ranked in tertiles. An experienced neuroradiologist, who was blinded to all clinical information, reviewed all images.

Administration of ECT

Patients received twice weekly ECT in accordance with Dutch standards (33). A course started with right unilateral ECT (RUL). All treatments were administered with the Thymatron System IV (maximum energy 200%, 1008 mCoulombs) using a titration dosing protocol. The stimulus intensity was determined by empirical dose titration at the first treatment, for RUL 6 times the initial seizure threshold (ST) and for bilateral ECT 1.5 times ST. All patients were treated with brief pulse ECT (0.5–1.0 ms) ECT. A motor seizure of less than 20 seconds was considered inadequate and the dose was subsequently raised according to Dutch guidelines (34). Switching to bilateral ECT was applied when the clinical condition worsened or when after 6 unilateral treatments there was no clinical improvement. Clinical evaluation was carried out weekly. Criteria for clinical worsening were: increase in total MADRS-scores, debilitating psychotic features, increased suicidality, dehydration and weight loss. ECT was continued until the patients achieved a MADRS score of less than 10 at two consecutive ratings with a week

interval, or stopped when patients showed no further improvement in clinical condition during the last 2 weeks of ECT sessions after a minimum of 6 unilateral and 6 bilateral sessions. Psychotropic medication was discontinued at least 1 week prior to ECT, or if deemed impossible, kept stable from 6 weeks prior to ECT and during the ECT-course.

Response and remission

Remission after ECT was defined as a MADRS score lower than 10 points after ECT at two consecutive weekly assessments. Response was defined as a decrease in MADRS scores of at least 50% (35). The number of ECT treatments was determined by the treating psychiatrist, as described above.

Ethical issues

The study protocol of MODECT has been approved centrally by the Ethical Review Board of the VU University Medical Center, and subsequently by the ethical review board of the Leuven University Hospital and conducted according to the declaration of Helsinki. Written informed consent was obtained from all patients at the start of the baseline assessment. The study was registered at www.ClinicalTrials.gov with identifier: NCT02667353.

Statistics

Data were analyzed using the Statistical Package of the Social Sciences (SPSS, version 21, SPSS Inc., Chicago, IL). To study whether inclusion at the two sites was similar, differences between Amsterdam and Leuven were studied. For demographic data, group differences in continuous variables were determined by independent t-tests. If a variable was not normally distributed after log-transformation, a Mann-Whitney test (MW) was used and a z-approximation was reported. Group differences in categorical variables were calculated using χ^2 –tests.

Next, differences between EOD and LOD were also studied by means of parametric and non-parametric analyses.

Bivariate and multivariate logistic regression analyses were performed in the complete group as well as in both onset groups separately, to investigate the relationship between clinical variables and response to ECT. We selected variables showing p-values < 0.05 as input for a multiple logistic regression model to evaluate their unique predictive value. In order to prevent multicollinearity, we computed the correlation coefficients between all independent variables. When the correlation coefficient was higher than .80, we did not include these variables in the same model. To study whether the association between clinical variables and response was the same for EOD and LOD, interaction (onset x clinical variable) terms were tested. A p-value of < 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

The baseline sample consisted of 110 severely depressed patients with a mean age of 73.0 years (SD 8.45), and consisted of 72 (66.1%) women (Table 1). Patients had used a median of two antidepressant treatments, thus establishing failure to respond to pharmacotherapy. The Leuven site included more patients with pharmacotherapy resistance as the primary indication (69.8 versus 50.7%), and the number of antidepressant medication trials was higher in Leuven (MW 0.035, table 1), however, the medication resistance score was not significantly different between the two sites (χ^2 8.39, df 5, p=0.136, table 1). In the Amsterdam sample there was more somatic comorbidity (χ^2 8.56, df 1, p=0.003, table 1); specifically cardiovascular disease (χ^2 7.90, df 1, p=0.005, table 1), and periventricular white matter hyperintensities (WMH) in the brain were more prominent (MW p=0.02, table 1).

Response rate in our sample was 78.2%. The response and remission rates were not statistically different between the two sites; ~~however there appeared to be a trend for better rates in Leuven~~ (response Leuven 86.0 vs. Amsterdam 73.1% (χ^2 2.56, df1, p=0.11, table 1), remission Leuven 76.7 vs. Amsterdam 59.7% (χ^2 3.41, df1, p=0.07, table 1). At the Amsterdam site the rate of switching to bilateral ECT was higher (χ^2 -2.68, df31, p= 0.01).

INSERT TABLE 1

Early- versus late-onset depression

Patients with LOD had a higher response rate (86.9% vs. 67.3%, χ^2 6.08, df 1, p=0.01, table 2), with similar number of ECT sessions (mean 11.0 (SD 4.9) in LOD vs. 12.8 (SD 6.2) in EOD, t 1.58, df 90.2, p=0.12, table 2). The clinical profile of LOD versus EOD was similar in terms of depressive and psychotic symptoms and medication resistance. Somatic comorbidity was not different between EOD and LOD and neither were the structural brain characteristics. Patients with EOD were younger (t-4.34, df 108, p<0.001, table 2), experienced more depressive episodes (MW 0.003, table 2) and more admissions (MW<0.001, table 2).

INSERT TABLE 2

Factors associated with response

Higher response rates in the total sample were bivariately associated with later age at onset (OR 2.80, 95%CI 1.11-7.07, Wald X^2 5.75, p=0.03, table 3), lower medication resistance score (OR 0.63, 95%CI 0.42 – 0.95, Wald X^2 4.84, p=0.03, table 3) and more psychotic symptoms (OR 3.22, 95%CI 1.21 – 8.55, Wald X^2 5.48, p=0.02, table 3). In multiple logistic regression

analyses high response rate remained associated with later age at onset (OR 3.06, 95%CI 1.07 – 8.70, Wald X^2 4.39, p=0.04) and more psychotic symptoms (OR 3.30, 95%CI 1.12 – 9.74, Wald X^2 4.67, p=0.03), but not with medication resistance score (OR 0.69, 95%CI 0.45 – 1.03, Wald X^2 3.24, 0.07) (data not shown). The multivariate model explained 21.8% of the variance in response versus non-response (χ^2 15.39, df 3, p =0.002).

In order to study whether the associations between predictors of response to ECT were different for LOD compared to EOD we examined the interaction terms EOD/LOD x predictor variable in the logistic regression models (Table 3) and performed stratified analyses according to age at onset status. The interaction terms "EOD/LOD x duration of index episode" and "EOD/LOD x medial temporal atrophy (MTA)" were statistically significant. Stratified analyses showed that in EOD, a shorter duration of index episode was associated with higher response rates (OR 0.92, 95%CI 0.86 – 0.98, Wald X^2 6.73, p=0.01, table 3) whereas in LOD no significant association was found. Furthermore, in EOD the odds for response were higher when having more hippocampal atrophy (OR 3.20 (0.73 – 14.1, Wald X^2 2.37, p=0.12, table 3), whereas the odds for response in LOD was higher when having less hippocampal atrophy (OR 0.49 (0.17 – 1.44, Wald X^2 1.70, p=0.19, table 3), however both associations were not statistically significant.

INSERT TABLE 3

Discussion

MODECT is a two-site prospective intervention study examining clinical outcome in EOD and LOD following ECT in 110 patients with severe LLD. Response rate was 78.2%, and similar between the two sites, but significantly higher in LOD compared to EOD (86.9 vs. 67.3%, p=0.01). The clinical profile, somatic comorbidities and structural brain characteristics were not different between EOD and LOD. Nevertheless, patients with LOD showed a superior response to ECT compared to patients with EOD. Response to ECT was associated with late age at onset and presence of psychotic symptoms, and not with structural brain characteristics. Our results indicate that ECT is very effective in LLD, even with vascular burden.

Sample

Patients had had a median of two antidepressant trails, confirming that ECT is very effective even in patients that failed to response to pharmacotherapy. Patients from the two sites were very comparable, however the Leuven site included more patients with pharmacotherapy resistance and in the Amsterdam sample there was more somatic comorbidity and the white matter hyperintensities were more prominent. The preponderance of somatic comorbidity in the Amsterdam sample might have led to a higher rate of switching form right unilateral to bilateral ECT. Indeed, physically frail patients very often show life threatening symptoms due to refusal of food and fluids, justifying the application of bilateral electrode position, given its more rapid symptom reduction (36).

The response rate was 78.2%, similar between the two sites, and at the higher end of the range previously reported in LLD (37). Response to ECT was associated with late age at onset and presence of psychotic symptoms, and not with structural MRI characteristics.

EOD versus LOD

In our sample of patients with severe LLD the clinical profile of EOD and LOD was very similar, as was shown in previous studies in clinical samples with severe depression (15, 38, 39). Symptom profile or severity, and duration of current episode were not different in EOD or LOD in our sample of severe LLD eligible for ECT. Contrary to our hypothesis, somatic comorbidity and structural brain characteristics were similar in EOD and LOD in our sample.

Patients with LOD had a higher response rate, compared to patients with EOD. ~~In EOD, there was a trend for medial temporal atrophy to be associated with higher odds for response in EOD, which was reversed in LOD.~~

Examining factors related to response in EOD and LOD, we found that in EOD response was associated with shorter duration of index episode (OR 0.92, 95%CI 0.86 – 0.98) but we failed to identify significant associations with response in LOD.

In EOD more medial temporal atrophy (MTA) was associated with higher odds for response, whereas in LOD less MTA was associated with higher odds for response. Although the interaction term "EOD/LOD x MTA" was statistically significant, the associations in the separate subsets (EOD and LOD) were not statistically significant. ~~MTA may have a different pathological mechanism in EOD and LOD. In EOD it may be a result of long-term exposure to high cortisol, whereas in LOD may reflect a prodromal phase of dementia (40).~~

In patients with severe LLD, age at onset is probably not identifying clinical subtypes.

Predicting response to ECT

We set out to identify predictors of response, more specific in LOD in order to explain its superior response rate in comparison to EOD.

In our total sample, psychotic symptoms and less medication resistance were associated with better response, but these factors were similar in EOD and LOD. This is in contrast with recent meta-analysis which failed to identify psychotic features as a positive predictor for ECT response (41). This finding may depend on several factors. Most studies were done in younger patients and the definition of psychotic features is not unequivocal. Moreover, psychotic depressed patients may receive ECT earlier in their course of illness and thereby have shorter episode and less medication resistance.

The presence of psychotic features based on clinical judgment was found to be a robust predictor of response to ECT in several previous studies (42-44). Previously, a study from our own group on LLD treated with ECT found that depression with psychotic symptoms was significantly associated with absence of cognitive decline after seven to 12 years of follow-up (45). Psychotic symptoms may be a unique feature enabling differentiation between older "truly" depressed patients and patients with depression symptoms as a prodromal stage of dementia.

In our sample the median duration of the current episode was 6 months, similar in EOD and LOD. In EOD a shorter duration of index episode was associated with higher response rates. In the aforementioned meta-analysis (41) duration of current episode, together with relative absence of medication failure was found to be a robust clinical predictor of response to ECT. In responders the current episode had a weighted mean duration of 6.6 months versus 14 months in non-responders (41). As in our sample, it seems likely that older patients receive ECT earlier in their course, as they may not tolerate pharmacotherapy. This may explain why age was not found to be a predictor for response to ECT in this meta-analysis contrary to previous findings (16, 17, 46).

Higher response rates to ECT were not associated with absence of somatic illnesses, presence of cardiovascular disease or structural brain characteristics. Recently, in LLD treated with pharmacotherapy, the association of cerebrovascular risk and poor treatment outcome in LLD

was reconfirmed (47). Cerebrovascular burden may hamper the effect of antidepressants in LLD. In our sample, before ECT, patients had had a median of 2 antidepressant trails, establishing failure to respond to pharmacotherapy. Yet, our results indicate that ECT is very effective even in pharmacotherapy-resistant LLD with vascular burden.
We were not able to explain the higher response rates in LOD by clinical of structural brain characteristics, the number of non-responders with LOD is probably too low (n=8) to find statistically significant associations.

Strengths and limitations

The strength of our study is that we were able to include a substantial number of older patients treated with ECT and collect a comprehensive set of clinical data on all patients, including brain imaging. In most aspects, the patients included from the two sites were similar. However, patients from the Amsterdam site had more somatic comorbidities and more vascular brain pathology, which is in line with the fact that the Amsterdam site is a tertiary referral center for ECT in frail severely depressed older patients. On the other hand, Leuven patients had higher medication resistance scores, which is in accordance with their referrals of pharmacotherapy resistant patients in the region.
The study was parallel, but subordinate to patient care and therefore, as some patients needed ECT before inclusion could be completed, some data (MRI scans, clinical scales) were missing. Nevertheless, 70 to 99% of clinical rating scales were completed and 72% of patients had a MRI scan before their first ECT. Data on age at first depressive episode were collected dichotomously, limiting analyses with age at onset as a continuous variable. Another limitation is that many statistical tests were performed resulting in an increased risk for Type I errors. In this study we chose to include structural brain characteristics using visual rating scales for well-known age-related changes. A comprehensive qualitative evaluation of imaging data was beyond the scope. For clinical interpretation, our relatively large sample of LDD inpatients is yet small compared to epidemiological studies and the homogenous nature may limit the generalization of our results. Hence, our findings may not be extrapolated to other populations, e.g. less severely depressed outpatients.

In conclusion, although response rates to ECT in our sample of patients with LLD was high, patients with LOD showed the highest response rates. This difference could not be explained by differences in clinical profile or structural brain characteristics. Our results provide also evidence for the notion that ECT is most effective in LLD with psychotic symptoms regardless of their age at onset of first depressive episode. Furthermore, we conclude that ECT is very effective in vascular burdened patients.

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