Towards an improvement of the differentiation of depressive disorders. A multidimensional approach

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4

Anxious-retarded depression: Relation to two-year outcome of major depressive disorder.

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Abstract

Background: Anxious-retarded depression is a two-dimensionally defined subcategory of depression derived from DSM-IV melancholia. It is related to increased plasma vasopressin, correlative plasma vasopressin and cortisol levels, and a positive family history. We now explored its relation with outcome. Methods: Seventy depressed patients were included to follow-up for two years. Outcome was defined by time until full-remission of depression. Cox regression analyses were used to compare patients with anxious-retarded and non-anxious-retarded depression, as well as melancholic and non-melancholic patients. Results: Anxious-retarded depression had a poor outcome. Limitations: The number of patients was small. Conclusion: The relation with poor outcome further supports the validity of the anxious-retarded subcategory.

Key words: Melancholia, dimensions, anxiety, psychomotor retardation, outcome

1 Introduction

An anxious-retarded subcategory of depression has been derived from DSM-IV melancholia by using a multidimensional structure of psychopathology (De Winter et al. 2004). The validity of this subcategory is supported by correlative plasma vasopressin (AVP) and cortisol levels, elevated plasma AVP (De Winter et al. 2003), and a relation with family history of depression (De Winter et al. 2004). The melancholic subcategory was less or not related to these parameters.

We now describe a next step of the validation programme proposed by Robins and Guze (Robins and Guze 1970), by investigating the long-term outcome of this anxious-retarded subcategory. Since anxious-retarded depression has been derived from melancholia, we additionally investigated the outcome in melancholic patients. Many factors have been found to predict poor outcome of depression: The melancholic subcategory (Tuma, 2000), endogenous depression (O'Leary 1996), symptom severity and duration of illness (Keller et al. 1992), retardation (van Londen et al. 1998), anxiety (Coryell et al. 1992), neuroticism (Scott et al., 1992), a positive family history of depression (Kendler et al. 1997), female gender (Sargeant et al. 1990), older age and lower education (Ronalds et al. 1997), family history of mental disorder (Duggan et al. 1998), and psychiatric and somatic co-morbidity (Keitner et al, 1991). In the present outcome study we investigated the role of these factors (except for the last two) as covariates of poor outcome. In addition we investigated the effect of insufficient treatment. Outcome was defined as the time to full-remission (Frank et al.1991).

2 Methods

2.1 Patients

The patient sample was a sub-sample of that investigated in preceding cross-sectional analyses (De Winter et al. 2003; De Winter et al. 2004). Inclusion criteria were DSM-IV major depression, Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979) score > 20, age 18-65 years, and first episode before the 60th years. A psychiatrist at the inpatient or outpatient clinic primarily made the diagnosis of major depression (DSM-IV). If R.F.P.de W. confirmed the diagnosis in an individual subject (see Section 2.2), the patient was asked to participate in the study. Inclusion and exclusion criteria have been published before (De Winter et al. 2003, De Winter et al. 2004). The Medical Ethics Committee of the Leiden University Medical Centre approved the research protocol. Written informed consent was obtained from each patient.

2.2 Assessment and outcome measures

Psychopathology was assessed with the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al. 1978) at the start of the study (t1), six weeks later (t2) and than after 3, 6, 12 18 and 24 months (t3 – t7)). All CPRS items were rated from 0 – 6, covering the two weeks preceding the assessment. DSM-IV criteria for major depression were assessed by using corresponding CPRS items. A score ≥ 3 was taken as representing the DSM-IV severity criterion of a symptom being more present than absent. Increased appetite and weight were rated separately. Full remission was defined by a maximum of 2 symptoms during at least the last 2 weeks. Partial remission was defined by a minimum of 3 and a maximum of 4 symptoms (Frank et al. 1991). DSM-IV subcategories were assessed by semi-standardized interviews.

The anxious-retarded subcategory was defined as the combination of above median scores for anxiety and retardation, assessed by two scales from the CPRS (Goekoop et al. 1992): autonomic dysregulation (≥11) and motivational inhibition (≥8) (De Winter et al. 2003). A positive family history was quantified by the presence or absence major

depressive disorder in any first degree using a slightly modified version of the Family History interview by Andreasen (Andreasen et al. 1986; De Winter et al. 2004). Neuroticism was assessed by Eysenck's Personality Questionnaire (Eysenck and Eysenck 1975). Educational level was classified in six categories (level 1 = no or low education until level 6 = university or postgraduate).
Depressive intensity was rated with the MADRS. Duration of current episode was assessed by history taking of the individual patient, and was defined by the number of months with preceding depressive symptoms. The number of episodes was also assessed by history taking. Each episode was defined by treatment necessity.

2.3 *Treatment*

Treatment was carried out after t1 according to a standardised treatment guideline comprising cognitive behavioural therapy or/and antidepressant drug treatment depending on severity, second antidepressant, lithium addition, MAO-inhibitor. Insufficient treatment was defined by the absence of antidepressant treatment when fully depressed (or not fully remitted), or the absence of antipsychotic treatment in a patient with psychotic depression. This insufficiency was quantified as the sum of the time points of its occurence.

2.4 *Data analysis*

Mann-Whitney U, *t* tests and χ^2 were used for differences between subgroups of patients. Kaplan-Meier curves were made and Cox regression analyses (forward stepwise) were used to test whether outcome differed between subcategories and their patient control groups, accounting for the effect of covariates. The Statistical Package for Social Sciences version (SPSS 9.0 INC, Chicago) was used for all analyses.

3 Results

Patients lost in the follow-up and those remaining in the follow-up did not differ on clinical or demographic parameters (neuroticism, number of previous episodes, duration of current episode, family history of depression, psychotic depression, atypical depression, melancholia and anxious-retarded subtype, or age, gender and education) (χ^2, *t* test or Mann-Whitney U, $P > 0.05$). There were also no clinical or demographic differences between the anxious-retarded or melancholic subcategories and their patient control groups (χ^2, *t* test or Mann-Whitney U, $P > 0.05$). From the 24 anxious-retarded patients 20 patients fulfilled criteria for the melancholic subcategory ($\chi^2 = 19.2$, df = 1 and $P < 0.0001$) and six had psychotic features ($\chi^2 = 3.42$, df = 1 and $P = 0.064$).

Figure 1 and Table 1 show rates of full remission and non-remission in anxious-retarded and non-anxious-retarded depression during follow-up. The patients with anxious-retarded depression differed significantly from all other patients in time to full remission (Wald = 7.85, df = 1 and p = 0.005). Analysis of covariate effects, including initial MADRS score, did not result in altered Wald and P values (Table 2). The strength of the relation between poor outcome and anxious-retarded depression was slightly reduced by insufficient antipsychotic (Wald = 6.634; df=1; p=0.010) or antidepressant (Wald 6.583; df=1; p=0.010) treatment as covariates. The use of both covariates resulted in the same Wald as the latter.

The dichotomised scores of initially high versus low anxiety, and high versus low retardation, were not related to time to full remission (Wald = 1.162, df = 1 and p = 0.204, and Wald = 2.080, df = 1 and p = 0.149), neither was melancholia related to this outcome measure (Wald = 3.21, df = 1 and p = 0.073).

Figure 1
Remission and MDD rates for anxious-retarded and non-anxious-retarded patients during follow-up

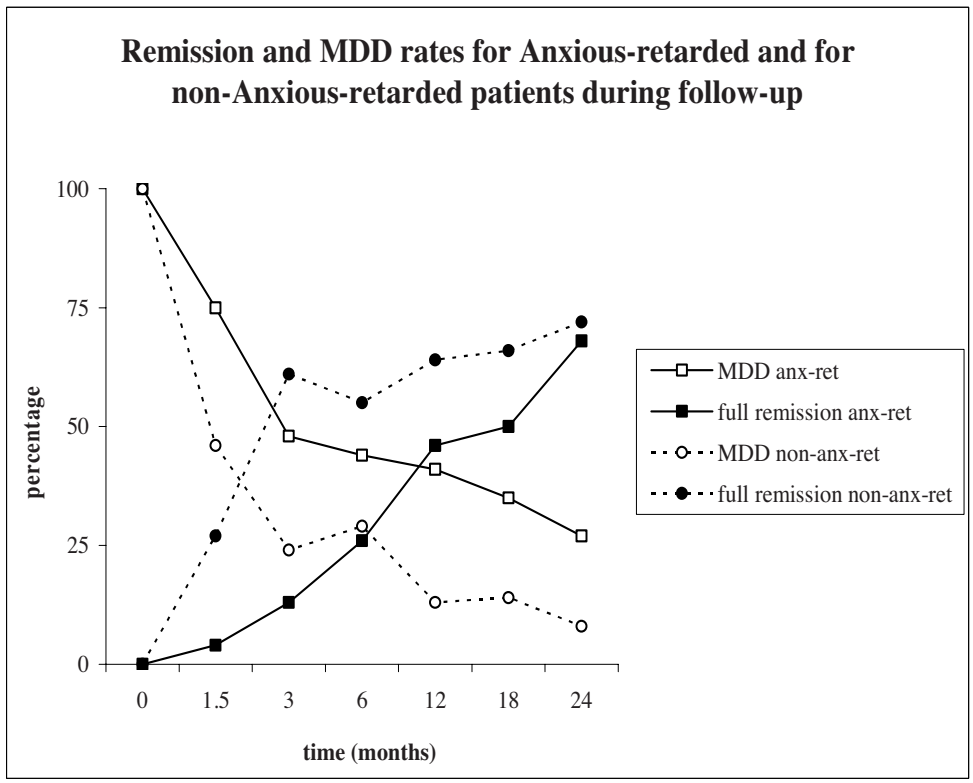

Table 1

Percentages of patients fulfilling criteria for MDD criteria, partial remission and full remission in all patients, patients with the melancholic subcategory and patients with anxious-retarded depression

MDD and subcategory	6 weeks percentage (n)	3 months % (n)	6 months % (n)	1 year % (n)	18 mnths % (n)	2 years % (n)
All patients:						
MDD	56% (37)	33% (21)	34% (22)	23% (14)	22 % (12)	16 % (9)
Partial remission	25% (16)	23% (15)	21% (14)	20% (12)	18% (10)	14% (8)
Full remission	19% (12)	44% (28)	45% (29)	57% (35)	60% (33)	71% (41)
Melancholic:						
MDD	69% (22)	40% (12)	39% (12)	27% (8)	19% (5)	18% (5)
Partial remission	25% (8)	33% (10)	32% (10)	27% (8)	15% (4)	14% (4)
Full remission	6% (2)	27% (8)	29% (9)	47% (14)	65% (17)	68% (19)
Anxious-retarded:						
MDD	75% (18)	48% (11)	44% (10)	41% (9)	35% (7)	27% (6)
Partial remission	21% (5)	39% (9)	30% (7)	14% (3)	15% (3)	5% (1)
Full remission	4% (1)	13% (3)	26% (6)	46% (10)	50% (10)	68% (15)
Non-anxious-retarded						
MDD	46% (19)	24% (10)	29% (12)	13% (5)	14% (5)	8% (3)
Partial remission	27% (11)	15% (6)	17% (7)	23% (9)	20% (7)	19% (7)
Full remission	27% (11)	61% (25)	55% (23)	64% (25)	66% (23)	72% (26)

Table 2
Wald values of relations between anxious-retarded depression as well as covariates and poor outcome.

Predictors	Wald	p
Anxious-retarded depression	7.85	.005
Age	0.26	ns
Gender	0.30	ns
Neuroticism	0.06	ns
Education	0.28	ns
Number of previous episodes	1.07	ns
Duration of current illness	0.10	ns
Family history	0.38	ns
Psychotic depression	0.22	ns
Melancholia	0.27	ns
Depression Severity (MADRS)	1.93	ns

4 Discussion

The anxious-retarded subcategory had a poor outcome in terms of time to full remission. Intensity of depression assessed by the MADRS did not affect this relation. Neither did the weak influences of insufficient antipsychotic and antidepressant treatment explain this relation.This multidimensionally defined subcategory is therefore now not only validated by by increased plasma vasopressin, correlative plasma vasopressin and cortisol levels (De Winter et al., 2003) and a positive family history (De Winter et al., 2004), but also by a poor outcome.

The combination of high anxiety and high retardation was required for this prediction, since the dichotomised scores for anxiety and retardation separately were not significantly related. The present results can be seen as adding information to previous findings relating anxiety or anxiety disorder comorbidity (Bakish, 1999; Clayton et al., 1991; Coryell et al., 1992) and retardation (Parker et al., 1992; van Londen et al., 1998) to poor outcome of depression.

In contrast with the non-anxious-retarded subgroup outcome in the anxious-retarded subcategory appeared not homogeneously distributed. After two years anxious-retarded patients were generally either fully remitted or still depressed. Only one patient was partially remitted (5%). Although the number of patients involved in this study is relatively small, these data suggest a differentiation of outcome specific for the anxious-retarded subcategory. The number of patients was also too small for the analysis of the confounding effect of the melancholic subcategory.

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