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Duration of untreated illness in schizophrenia is not associated with 5-year brain volume change

Geartsje Boonstra *, Wiepke Cahn, Hugo G. Schnack, Hilleke E. Hulshoff Pol, Tanca C. Minderhoud, René S. Kahn, Neeltje E.M. van Haren

Department of Psychiatry, University Medical Center Utrecht, P.B 85500, 3508 GA, Utrecht, The Netherlands

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ABSTRACT

Objectives: Evidence for an association between duration of untreated illness (DUI) with clinical and functional outcome or brain volume (change) in schizophrenia patients is inconclusive. We aimed to investigate the relationship between DUI, outcome and brain volume at illness onset or brain volume change during the first five years of the illness in first-episode patients.
Methods: Magnetic resonance images were acquired at baseline (T0) and after 5-year (T5) of 57 schizophrenia patients. Correlations were calculated in patients between brain volume (change), DUI and outcome variables.
Results: We found no significant correlation between DUI and brain volume (change) in schizophrenia patients. A longer DUI was significantly correlated with higher PANSS scores at T0 and T5, and with higher scores on the Camberwell Assessment of Need scale at T5. Baseline volume of the cerebrum and lateral ventricles, and cerebellum volume (change) were associated with PANSS scores at T0 and T5.
Conclusion: Although clinical outcome is associated with both brain volume (change) and DUI, we found no evidence for a relationship between DUI and brain volume (change). DUI and baseline brain volume or 5-year brain volume (change) seem to explain different parts of the variation in clinical outcome.

1. Introduction

Schizophrenia is, in the majority of cases, characterized by an insidious onset, often preceded by a decline in functioning. Duration of untreated psychosis (DUP), prodrome (DPD) and untreated illness (DUI) have all been used to characterize the period before the start of treatment or the onset of psychosis. DUP is the time between onset of psychosis and the start of treatment, which is generally defined as hospitalization (Madsen et al., 1999; Perkins et al., 2005; Bangalore et al., 2009) or (adequate) antipsychotic treatment (Perkins et al., 2005; Crespo-Facorro et al., 2007a; Selten et al., 2007; Emsley et al., 2008; Crumlish et al., 2009). Onset of psychosis is usually determined retrospectively and is defined as the onset of first psychotic symptoms (Perkins et al., 2005; Lappin et al., 2006; Crespo-Facorro et al., 2007a; Selten et al., 2007; Emsley et al., 2008; Bangalore et al., 2009).

The start of DPD is usually defined as a persistent deviation from the individual's normal premorbid functioning, behavior or personality and/or the emergence of prodromal psychiatric symptoms that do not fulfill the criteria for psychosis (Loebel et al., 1992; Crespo-Facorro et al., 2007a; Bangalore et al., 2009; Crumlish et al., 2009; Ebdrup et al., 2010; O'Callaghan et al., 2010). It ends at the emergence of psychotic symptoms. Finally, DUI is defined as the sum of DUP and DPD.

Clinical and social outcome variables have been associated with DUI (Loebel et al., 1992; Crumlish et al., 2009; Owens et al., 2010) and DPD (Malla et al., 2002; Harrigan et al., 2003; Fusar-Poli et al., 2009) in that longer DUI or DPD correlated with poorer outcome. However, others could not replicate such a relationship (Barnes et al., 2000; Craig et al., 2000; Ho et al., 2000; Hoff et al., 2000; Norman et al., 2001; Malla et al., 2002; Harrigan et al., 2003; Selten et al., 2007; Gonzalez-Blanch et al., 2008). A small to moderate effect of DUP on outcome in schizophrenia, including symptom remission and functional rehabilitation has been established in two reviews (Marshall et al., 2005; Perkins et al., 2005).

Interestingly, poorer outcome has also been associated with smaller brain volumes (Buchsbaum et al., 2003; Molina et al., 2010), larger ventricles (DeLisi et al., 2004) and excessive brain volume loss over time (Cahn et al., 2002; Cahn et al., 2006; Van Haren et al., 2008), for review see (Hulshoff Pol and Kahn, 2008; Kempton et al., 2010). Therefore, we hypothesize that DUP, DUI or DPD through their effect on outcome, are associated with (change in) brain volume abnormalities in schizophrenia patients or vice versa. Consequently, a longer delay of treatment would be related to larger decline of brain volume. Indeed, cross-sectional studies provide evidence for an association between brain abnormalities and a longer DUP, DUI or DPD (Angelopoulos et al., 2002; Bangalore et al., 2009; Crespo-Facorro

* Corresponding author at: ACT1 team, Department of Psychiatry and Addiction, WA-huis, Altrecht GGZ, Lange Nieuwstraat 119, 3512 PG, The Netherlands. Tel.: +31 30 2308802; fax: +31 30 2308668.
E-mail addresses: g.boonstra@altrecht.nl (G. Boonstra), w.cahn@umcutrecht.nl (W. Cahn), h.schnack@umcutrecht.nl (H.G. Schnack), h.e.hulshoff@umcutrecht.nl (H.E. Hulshoff Pol), t.c.minderhoud@asz.nl (T.C. Minderhoud), r.kahn@umcutrecht.nl (R.S. Kahn), n.e.m.vanharen@umcutrecht.nl (N.E.M. van Haren).

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et al., 2007a,b; Ho et al., 2003; Keshavan et al., 1998; Lappin et al., 2006; Madsen et al., 1999; Penttila et al., 2010; Takahashi et al., 2007; Théberge et al., 2004). So far, only one longitudinal study investigated the relationship between DUP, outcome and global brain volume change over time using computed tomography (CT), and found no evidence for such a relationship (Madsen et al., 1999). The advantage of longitudinal studies is that repeated observation in the same individual are obtained and these may have more power than observations from cross-sectional studies do.

The present study aimed to investigate the relationship between DUI, global brain volume (change), and outcome in first-episode schizophrenia patients.

2. Materials and methods

2.1. Subjects and design

Patients, aged 17–40 years, with a maximum antipsychotics exposure of 6 months, were recruited from The First Episode Schizophrenia Research Program at the University Medical Center, Utrecht, The Netherlands. After complete description of the study written informed consent was obtained from all participants. The Medical Ethics Review Board of the University Medical Centre Utrecht approved the study. This study was performed in accordance with the Declaration of Helsinki. Patients who had an MRI scan at inclusion (T0) and who were diagnosed according to DSM-IV criteria with schizophrenia at follow-up (T5) were included. Diagnosis was assessed with the Comprehensive Assessment of Symptoms and History Schizophrenia (Andreasen et al., 1992). The Positive and Negative Syndrome Scale (PANSS) was performed at T0 and T5 (Kay et al., 1987, 1988). At T5 both the Global Assessment of Functioning (GAF) and the Camberwell Assessment of Need (CAN) were performed (Endicott et al., 1976; Goldman et al., 1992; Phelan et al., 1995). Course of illness data to determine DUI was collected retrospectively using patient reports prompted by key data and data from a shortened version of the Interview for the Retrospective Assessment of the Onset of schizophrenia (IRAOS) at T5 (Hafner et al., 1992). Furthermore, a careful examination of the medical records was carried out and the treating psychiatrist and/or key worker were interviewed.

The duration of untreated illness (DUI) was defined as the period from onset of prodrome to the start of antipsychotic treatment. Criterion B from the DSM-III was used to define onset of prodrome (when one or more major areas of functioning such as work, interpersonal relations, or self care are markedly below the level achieved prior to the onset). Consensus was reached between two independent researchers (WC and TCM) about the date the prodrome started.

To calculate the lifetime cumulative dosage of antipsychotic medication up to T0 and T5, a careful examination of the medical records was carried out. A table from the Dutch National Health Service was used to derive the haloperidol equivalents for typical antipsychotics (No authors listed, 2007) (conversion rates: broomperidol 1:1, droperidol 1:1, haloperidol 1:1, penfluridol 1:1, perfenazine 5:1, pimozide 0.85:1, pipamperon 50:1, zuclopentixol 5:1). For atypical antipsychotic medication, the respective pharmaceutical companies suggested conversion rates into haloperidol equivalents (H-EQ) (clozapine, 40:1; olanzapine, 2.5:1; quetiapine, 50:1; risperidone, 1:1; sulpiride, 170:1).

In addition, 56 controls were included, group-matched for age, gender and handedness, in order to assess whether this patient sample shows the expected brain abnormalities (i.e., smaller cerebral (gray matter) volume at baseline, and excessive gray matter volume loss over time in patients relative to controls).

2.2. MRI data acquisition

Magnetic resonance images (MRIs) were acquired using a 1.5 Tesla Philips NT scanner. Volume measures of the intracranium, total brain (TB), cerebral gray (GM) and white matter (WM), cerebellum (CB), third (V3) and lateral ventricles (LV) were determined. Acquisition parameters and processing have been described previously (Schnack et al., 2001a,b; Van Haren et al., 2003) All segmentations were checked and corrected manually if necessary. The interrater reliabilities of the volume measurements, determined by the ICC were 0.95 and higher.

2.3. Data-analysis

Data were checked with the Pearson's Chi-Square test for nominal variables, ANOVA for normally distributed, and Mann–Whitney *U* test for abnormally distributed continuous variables (Table 1). Brain volume (change) was corrected for IC, age and gender using multiple regression analyses. Unstandardized residuals were saved and used in the main analysis. The difference in volume (change) between patients and controls was tested using ANOVA for normally distributed, and Mann–Whitney *U* test for abnormally distributed volume variables. Pearson's correlation coefficients, or Spearman Rank correlation coefficients in not-normally distributed variables, were calculated to investigate the association between 1) DUI and corrected brain volume (change) 2) clinical outcome measures (PANSS total and subscores at T0 and T5, GAF and CAN professional total score at T5) and DUI, and 3) clinical outcome measures and corrected brain volume (change). The significant associations were corrected for intake of alcohol or drugs in the three months prior to the study with partial correlations.

At baseline, 36 patients were medication-naïve and correlation analyses on baseline measures of outcome, brain volume and DUI were performed in this subgroup to exclude the influence of medication effects.

SPSS18 was used for all analyses. Only findings with $p<0.01$ are presented.

3. Results

3.1. Brain volume (change) in patients and controls

At baseline V3 was larger in patients compared to controls. Patients, compared to controls, showed a more pronounced loss of GM over a five year interval (Table 1).

3.2. DUI and brain volume (change)

No significant correlations were found between brain volume (change) and DUI (Table 2).

3.3. DUI and clinical outcome

Significant associations were found between DUI and clinical and functional outcome, indicating larger DUI to be related to poorer outcome (Table 2, Fig. 1). Longer DUI was significantly correlated with higher PANSS total scores at T5 ($\rho = .42$, $p = .003$), PANSS positive score at T0 and T5 (T0: $\rho = .37$, $p = .008$, T5: $\rho = .53$, $p = .00009$) and the PANSS general score at T5 ($\rho = .37$, $p = .01$). Furthermore, there was a positive correlation between DUI and the CAN total score at T5 ($\rho = .41$, $p = .004$).

3.4. Brain volume (change) and clinical outcome

Significant correlations were found between brain volume (change) and level of symptoms at baseline and follow-up measurement (Table 2). There was a negative correlation between baseline TB and the negative PANSS score at T0 and T5 (T0: $r = -.44$, $p = .002$; T5: $\rho = -.40$, $p = .005$). CB change was negatively correlated with the PANSS general score at T0 ($r = -.43$, $p = .01$). These correlations suggest that the presence of more symptoms is related to more CSF and less brain