Cholinergic deficiency and inflammation in cognitive dysfunction
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Citation for published version (APA):

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Chapter 3

Identification of responders to rivastigmine:
a prospective cohort study

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Dement Geriatr Cogn Disord. 2007;25(1):60-66
ABSTRACT

Although the overall effects of cholinesterase inhibitors (CEIs) are limited, there could be a subpopulation of patients who experience unequivocal benefit. This study aimed to describe a clinical profile based on a combination of specific neuropsychological test scores and clinical symptoms associated with a favourable response to rivastigmine.

A prospective cohort study was conducted in 53 patients who started rivastigmine treatment. Neuropsychological evaluation was performed at baseline and after 6 months of treatment. Patients were labelled responders and non-responders based on change scores after 6 months in 3 clinical domains: cognition, activities of daily living and behaviour.

After 6 months 19 responders and 15 non-responders were identified. Variability in reaction time and Continuous Performance Test (CPT) scores differed significantly at baseline between groups. A previously defined cluster of 4 items of the Neuropsychiatric Inventory was correlated with therapeutic response.

These findings suggest that patients who respond well to CEI therapy can be identified by deficits in attention, combined with a cluster of behavioural symptoms, including hallucinations, apathy, anxiety and psychomotor disturbances. This may constitute the clinical profile of cholinergic deficiency. Further prospective studies in larger populations are warranted to investigate if this profile can be used to select patients who will benefit from CEIs.
INTRODUCTION

Cholinesterase inhibitors (CEIs) are widely prescribed for patients with cognitive deficits. Randomised controlled trials established modest therapeutic effects of these drugs in Alzheimer’s disease (AD), Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD). However, the therapeutic response to CEIs and the severity of side effects vary widely between patients. This has fuelled discussions on licensing and reimbursement of CEIs in several countries. In the UK e.g., the National Institute for Health and Clinical Excellence (NICE) recommends CEIs only for a subgroup of AD-patients, namely only those with moderate disease severity. This vigorously discussed decision points to a more general awareness that the original license for CEIs, namely dementia defined in global terms, may not be the most appropriate target of this class of drugs. However, to date the subgroup of patients that suffer from (cholinergic) deficits that are amenable to treatment with CEIs cannot be clearly delineated on clinical grounds. In an early retrospective study, Mega et al. pointed out that a pre-treatment behavioural profile may be helpful in predicting a response to donepezil. Several other studies investigated possible predictors of a favourable CEI response: clinical characteristics such as disease severity, fluctuating cognition, a diagnosis of DLB or PDD, and older age have been described as possible predictors of beneficial therapeutic response in retrospective studies. Based on post-hoc analyses of trial data in various populations it is proposed that patients with visual hallucinations and specific behavioural symptoms as described by clusters of items of the Neuropsychiatric Inventory (NPI) are more likely to respond to CEI treatment. A prospective cohort study linked response to attentional deficits as measured by the Digit Symbol Substitution Test. A recent study by Saumier et al. showed that response to donepezil in AD patients was predicted by a better performance on visual-spatial motor tasks and the Boston naming test. Neurophysiological measures and findings on neuroimaging could also have some association with response to CEI therapy, but these techniques are not widely applicable yet.

The observations described above indicate that although overall effect of CEIs in unselected groups of patients may be limited, there could be a specific subpopulation of patients with a more satisfactory response than has been reported up till now in clinical trials. The question is: how can these patients can best identified in clinical practice? We proposed earlier that a neuropsychiatric syndrome may be delineated that develops as a consequence of cholinergic deficiency in the central nervous system. Based on early reports in psychiatric literature on effects of anticholinergic medication, this cholinergic deficiency syndrome can be characterised clinically by attentional deficits, anxiety and confusion with hallucinations and
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delusions\textsuperscript{21,22}. Potentially, this cholinergic deficiency syndrome can occur in any neurodegenerative disease affecting the cholinergic system and it may be associated with a specific profile of cognitive deficits. The cholinergic deficiency syndrome may offer a more rational indication for CEI treatment than a specific disease category or subgroups of patients arbitrarily defined by a range of Mini Mental State Examination (MMSE) values.

In this study, our goal was to describe the clinical profile that is associated with a favourable response to rivastigmine, based on a combination of neuropsychological impairments and clinical symptoms, regardless the underlying nosological entity. This profile could be helpful in discerning patients with a high level of cholinergic deficiency who will benefit most from therapy with CEIs.

METHODS

Patients

A prospective cohort was recruited between January 2002 and January 2006, from the outpatient clinics of the Academic Medical Centre in Amsterdam, the Medical Centre Alkmaar in Alkmaar and Parnassia Psycho-medical Centre in The Hague. Patients were included when they had suffered from progressive cognitive decline for more than 6 months as reported by patient, caregiver and referring physician. Cognitive decline had to be accompanied by neuropsychiatric features, because the prior probability of suffering from significant cholinergic deficits in these patients was estimated to be higher than in an unselected group of patients solely defined by dementia. This assumption is based on experiments with anticholinergic drugs in the past which conveyed that an anticholinergic state resembles closely the clinical picture of delirium\textsuperscript{20-22}.

Patients were required to have contact with a responsible caregiver on at least 5 days a week. The referring physician decided if there was an indication for therapy with rivastigmine. When the study was designed, rivastigmine was the only licensed CEI available in the Netherlands. Exclusion criteria were: a MMSE score of less than 12\textsuperscript{23}; bedridden; asthma; fever; metabolic disorders; pre-existing psychiatric disease or other causes that could explain the cognitive symptoms; use of neuroleptics, anticholinergic medication or previous use of cholinesterase inhibitors; alcohol or drug misuse.

This study was approved by the local ethical committees. Patients and their caregivers gave written informed consent before entering the study.
Identification of responders to rivastigmine

Evaluation

All patients referred for the study underwent routine physical and neurological examination by one of the investigators (AWL). Diagnoses made by the referring physician were verified by using the appropriate international classification criteria for the specific diseases (AD: NINCDS-ARDA\textsuperscript{24}; Vascular dementia (VaD): NINDS-AIREN\textsuperscript{25}; DLB: consensus criteria suggested by the consortium on DLB\textsuperscript{26}; PDD: established Parkinson’s disease according to UK Parkinson’s disease brain bank criteria\textsuperscript{27} in combination with dementia according to Diagnostic and Statistical Manual of Mental Disease (fourth edition) – criteria\textsuperscript{28}). Routine laboratory tests were performed (ESR, haemoglobin, WBC, thromocytes, sodium, potassium, creatinine, ureum, liver enzymes, glucose, cholesterol, TSH, vitamin B1 & B12, folic acid, syphilis serology) to exclude other causes for neuropsychiatric symptoms. Patients were evaluated clinically by the same neurologist (AWL) at baseline, at 3 months and 6 months after receiving rivastigmine. Clinical tests included: MMSE; Interview for Deterioration in Daily Living (IDDD), an 11-item paper-and-pencil questionnaire, which is completed by the caregiver, covering self-care activities such as dressing and eating, and complex instrumental activities such as shopping and taking care of financial affairs, total scores range from 0 (no assistance required for any activity) to 44 (always assistance required for all activities)\textsuperscript{29}; Neuropsychiatric Inventory (NPI), a widely used measure of dementia-associated neuropsychiatric disturbances\textsuperscript{30}; Unified Parkinson Disease Rating Scale-Motor part (UPDRS-III)\textsuperscript{31}; and the Clinician Assessment of Fluctuation (CAF), a series of screening questions regarding fluctuating confusion and impaired consciousness, producing a severity score from 0-12 (0 representing no fluctuating confusion, 12 representing severe fluctuating confusion)\textsuperscript{32}. Medication doses and side effects were noted separately. A standardised, partially computerised neuropsychological evaluation was performed independently by a neuropsychologist, who was not aware of the findings of the neurologist, at baseline, and 3 and 6 months after therapy. The following neuropsychological tests were included: Stroop-test (I, II and III)\textsuperscript{33}, simple visual reaction time measurement (VRT), part of the FePsy computerized neuropsychological test battery\textsuperscript{34,34}; Expanded Mental Control Test (EMCT) consisting of 12 serial items of increasing difficulty\textsuperscript{35}; Continuous Performance Test (CPT), an adaptation from the Paced Auditory Serial Addition Task (PASAT)\textsuperscript{36} and the Visual Association Test (VAT)\textsuperscript{37}. These tests were selected for their specific characteristics. The Stroop test, VRT, EMCT and CPT were selected for their ability to detect deficits in selective attention, mental processing speed, sustained attention and vigilance. As a control task we included a task that we did
not expect to correlate cholinergic deficits or with treatment response: the VAT, a measure of associative memory.

Analysis
After 6 months of therapy with rivastigmine patients were divided into 2 groups, respondents and non-responders. Unequivocal responders were patients who showed no change or an improvement of change scores after 6 months in all 3 clinical domains: cognition (MMSE), activities of daily living (IDDD) and behaviour (NPI). Although we did not include a subjective measure of response, we believe that the criterion of consistency among all change scores in 3 domains reliably reflects true benefit of the treatment. Patients who did not fulfil this criterion were labelled as non-responders. This also included patients who had only a partial response, for example improvement on the MMSE and NPI, but worsening on the IDDD. We choose not to divide the study-population in more than two groups because of the limited number of patients in our study.
The UPDRS-score was used to evaluate progression of parkinsonism. Neuro-psychological test scores at baseline, NPI items and CAF-scores at baseline were compared between the responders and the non-responders to find potential predictors for response.
Two clusters of NPI-items were evaluated that have been suggested to be associated with favourable therapeutic response before: the NPI-items 2, 3, 7 &10 (hallucinations, anxiety, apathy & abnormal motor behaviour) defined by Herrmann et al and a cluster of NPI-items 1, 2, 4 & 7 (delusions, hallucinations, depression and apathy) as suggested by McKeith et al3,11.

Statistical analysis
Statistical analysis was performed using SPSS 11.0 package for Windows. Data were tested for normal distribution. For not normally distributed numerical data Mann-Whitney U test was used to compare variables between groups, otherwise Student’s t-test was applied. In order to obtain a single value reflecting the overall change in the severity of dementia for individual patients, change scores on MMSE, IDDD and NPI were transformed to z-scores and a mean z-score of change of dementia severity was calculated. This sum z-score was used to analyse relationships between relevant variables and response using correlation and regression analysis, in addition to the responders/non-responders dichotomy. A value of \( P <0.05 \) was considered statistically significant for all statistical analyses.
RESULTS

A total of 68 patients were referred for the study and screened (see figure 1). Fifty-six patients were eligible of which 3 withdrew consent before starting rivastigmine therapy. DLB and PDD were the most prevalent diagnoses in this study population (Table 1). During treatment, a total of 10 (19%) patients dropped out due to adverse events, of which gastrointestinal symptoms were most frequently observed. The final analysis was performed on the data of 34 patients who completed 6 months of rivastigmine treatment. The baseline data of these patients are comparable to the data of the whole group at the beginning of the study (53 patients + 3 patients who withdrew consent before starting with the treatment) with respect to age (mean 71.4 yrs) gender M:F = 44:12), and MMSE-score (21, range 14-28).

Responders versus non-responders

Patients were labelled responders and non-responders to rivastigmine according to the responder-criteria as defined in the method section. Of the 34 patients, 19 patients showed improvement or no change in all three domains; only one patient had a change score of 0 on the MMSE and two patients had a change
score of 0 on the IDDD; all other 54 change scores were positive in these patients. This is a response rate of 56%, according to the strict criteria of the present study. The remaining 15 patients were non-responders (Table 1).

Of the responders, about half of the patients had a clinical diagnosis of probable DLB. In the group of non-responders there were 4 DLB-patients, 8 PDD-patients, 2 AD-patients and 1 patient with vascular dementia. There was a difference in mean age between the responders and non-responders (75.3 and 66.4 years, respectively; see also section below). After 6 months of therapy there was no difference in change on the UPDRS (p = 0.257) which could have explained deterioration on the IDDD in some of the non-responders.

Fluctuation in cognitive function as measured by the CAF did not differ between responders or non-responders at baseline or after therapy. However, for the whole group the CAF improved after 6 months of rivastigmine therapy (p = 0.002).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of responders and non-responders</th>
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<tbody>
<tr>
<td>Responders (n=19)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>Age, yrs (range)</td>
</tr>
<tr>
<td>Sex, M:F</td>
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<tr>
<td>Diagnosis*</td>
</tr>
<tr>
<td>AD</td>
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<tr>
<td>PDD</td>
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<tr>
<td>DLB</td>
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<tr>
<td>VaD</td>
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<tr>
<td>MMSE*, median (range)</td>
</tr>
<tr>
<td>IDDD*, median (range)</td>
</tr>
<tr>
<td>NPI*, median (range)</td>
</tr>
<tr>
<td>UPDRS*, median (range)</td>
</tr>
<tr>
<td><strong>Change scores at 6 months</strong></td>
</tr>
<tr>
<td>Δ MMSE, median (range)</td>
</tr>
<tr>
<td>Δ IDDD, median (range)</td>
</tr>
<tr>
<td>Δ NPI, median (range)</td>
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</tbody>
</table>

* AD: Alzheimer’s disease; PDD: Parkinson’s disease dementia; DLB: Dementia with Lewy Bodies; VaD: vascular dementia; MMSE: Mini Mental State Examination; IDDD: Interview for Deterioration in Daily living; NPI: Neuropsychiatric Inventory; UPDRS: Unified Parkinson’s Disease Rating Scale

** + = true positive change, indicating improvement; - = true negative change, indicating worsening
Mean dose of rivastigmine at 3 months was 8.1 and 7.9 mg and at 6 months 8.8 and 9.6 mg for responders and non-responders, respectively. Side effects probably related to rivastigmine were reported 15 times in 8 responders and 11 times in 10 non-responders. Nausea was the most frequent complaint. None of these side effects were severe. Atypical neuroleptics were taken by 2 patients, 1 in each group, benzodiazepines were taken by 5 patients in the responder-group (all sleeping tablets) and by none in the nonresponder-group, and SSRI’s were taken by 2 of the responders and by 3 of the non-responders.

Neuropsychological tests
Baseline test-scores of the VRT, its standard deviation in individual patients (VRT-sd), Stroop 1, 2 & 3, CPT, EMCT and the VAT were compared between responders and non-responders using the Mann-Whitney U test. Median scores and significance levels are displayed in Table 2.

Table 2. Baseline neuropsychological test-scores in responders and non-responders

<table>
<thead>
<tr>
<th></th>
<th>VRT*</th>
<th>VRT-sd*</th>
<th>Stroop1</th>
<th>Stroop2</th>
<th>Stroop3</th>
<th>EMCT*</th>
<th>CPT*</th>
<th>VAT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>525.5</td>
<td>733.5</td>
<td>86</td>
<td>138</td>
<td>655</td>
<td>14</td>
<td>58</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(281-3578)</td>
<td>(114-1504)</td>
<td>(56-370)</td>
<td>(52-302)</td>
<td>(162-885)</td>
<td>(2-24)</td>
<td>(31-61)</td>
<td>(0-12)</td>
</tr>
<tr>
<td>NR</td>
<td>388</td>
<td>325</td>
<td>64</td>
<td>100</td>
<td>320</td>
<td>14</td>
<td>61</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>(240-4000)</td>
<td>(41-1392)</td>
<td>(36-218)</td>
<td>(63-262)</td>
<td>(78-885)</td>
<td>(2-24)</td>
<td>(46-61)</td>
<td>(1-12)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.212</td>
<td><strong>0.015</strong></td>
<td>0.103</td>
<td>0.111</td>
<td>0.171</td>
<td>0.647</td>
<td><strong>0.022</strong></td>
<td>0.162</td>
</tr>
</tbody>
</table>

R = responders, NR = non-responders; displayed are median and (range)
* VRT = visual reaction time; VRT-sd = VRT-standard deviation; EMCT = expanded mental control test; CPT = continuous performance test; VAT = visual association test

Significant differences in baseline test-scores for responders and non-responders were found for the VRT-sd and the CPT (respectively, 0.015 and 0.022). The median VRT-sd of the responders was more than twice as high as of the non-responders, indicating a much higher intra-individual variability in reaction times. Together with lower CPT scores this suggests poorer sustained attention abilities in the responder-group. No distinct differences were found for the other neuropsychological tests the VRT, Stroop 1, 2 & 3, EMCT and VAT. Baseline median scores in VRT, VRT-sd, Stroop3, CPT and change over time in both groups are shown in figure 2. Figure 2 clearly shows that there is not only a difference at
baseline but also more improvement over time on the VRT-sd and CPT in the responder-group.

Based on z-scores for the change on the 3 clinical outcome scales a mean z-score was calculated for individual patients. This mean z-score (Zsum) as an overall measure of therapeutic response correlated with the baseline scores of both the VRT-sd ($\rho = 0.48; p=0.005$) and CPT ($\rho = -0.44; p=0.010$). There was no significant correlation between Zsum and age (Pearson’s $r = 0.241; p = 0.170$).

**NPI-clusters**

We compared the two predefined NPI-clusters and total NPI-score between responders and non-responders at baseline using Mann-Whitney U non-parametric tests. None of these three measures were significantly different between responders and non-responders, but for the cluster described by Herrmann et al.\textsuperscript{11} (NPI-items hallucination, anxiety, apathy and abnormal motor behaviour), there was a trend towards higher baseline scores in responders ($p = 0.079$). Exploring the correlation of this cluster with response as indicated by Zsum, using Spearman correlation coefficient, we found a positive correlation of 0.378; $p = 0.027$.

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**Figure 2.** Graphic display of 4 tests of the neuropsychological test battery. Changes of median scores in time from baseline at 3 and 6 months in responders and non-responders are shown. VRT-sd and CPT scores were significantly different at baseline between the groups. Vertical bars indicate interquartile range (25%-75%).
DISCUSSION

This was a prospective cohort study in patients treated with rivastigmine aimed at the delineation of a baseline clinical profile that predicts a beneficial response to CEI-therapy. Neuropsychological tests scores and clinical symptoms were used to define this clinical profile. Since cholinergic neuronal loss occurs in various degenerative diseases causing dementia we did not limit our study to a single disease entity. In this study strict criteria were applied in order to distinguish clinical relevant response to treatment. Our results show that fluctuations in reaction time tasks and poor sustained attention at baseline are features that are associated with a favourable response to treatment with rivastigmine. In the course of rivastigmine treatment the large baseline differences in attentional performance between responders and non-responders disappeared (figure 2). This supports the idea that the impairments as reflected in these two measures are sensitive to the effect of cholinesterase inhibition. Moreover, our results suggest that a cluster of behavioural symptoms, including hallucinations, apathy, anxiety and psychomotor disturbances, coexists with these attentional deficits in patients that respond well to CEI therapy.

The findings of this study agree with previous hypotheses and observations that cholinergic deficiency is best identified by impairments in attention and concentration accompanied by features such as confusion and hallucinations. In the few clinical trials on efficacy of CEIs that assessed behavioural symptoms and attention as primary outcome measures, beneficial effects in favour of CEI treatment-groups were observed. The presence of hallucinations predicted greater improvement in attention in DLB. In PDD-patients treatment effects were more marked if patients suffered from hallucinations. The fact that we were able to find strong correlations between baseline VRT-sd and CPT and, to a certain degree, between NPI-items at baseline and subsequent therapeutic response even in a small study population as in the present study support these notions. The small number of patients may render some of our conclusions prone to a type II error: some of the baseline differences that did not reach statistical significance may do so in the studies of larger patient groups. For example, in contrast to previous reports we did not find a difference in fluctuating cognition as measured by the CAF.

The same may hold for the fact that the correlation between age and therapeutic response (expressed by Zsum) was not significant, although mean age was higher in the group of responders. Van der Putt et al. described earlier a baseline difference in age between responders and non-responders, in which responders to CEI-treatment were older. This effect of age may imply that attentional deficits and behavioural disturbances are more prominent in older patients with dementia.
Our conclusions are based on correlation analysis. Due to the small cohort no reliable cluster analysis or regression modelling could be performed to obtain stronger evidence of specific features that are independently associated with response to CEIs. Further prospective studies in larger cohorts need to be performed for this purpose. To improve face-validity these future studies should preferably be carried out in heterogeneous populations which have a more representative distribution of dementias than our study did.

In our study the drop-out rate was lower than the rates reported in clinical trials and also the overall response rate was considerably higher (>50%) than reported in randomised trials\textsuperscript{2,3,42,43}. These effects are probably due to the specific selection of patients that were included in the present study. Although worsening of parkinsonism, especially tremor, due to use of cholinesterase inhibitors has been described, we found no significant difference in change of UPDRS scores over 6 months' treatment between the two groups\textsuperscript{44,45}.

Our study was a hypothesis-driven exploration to seek a clinical profile that may serve as a more sensible and reliable target for CEI-therapy than a nosological entity per se or subgroups of patients within an arbitrarily defined range of MMSE scores, as suggested by the recent NICE guidelines. This small open-label study has limited value in defining this profile in very specific terms but gives a hint of the direction that can be taken to explore new ways of administering CEIs in a group of patients suffering from very disturbing symptoms. Independent prospective studies in larger cohorts of patients, with various neurodegenerative diseases should be performed to determine the true value of this or similar risk profiles. Ideally, this should converge to a specific clinical profile in patients with cholinergic deficiency, which can be easily recognised by a small set of simple tests in the physician's office.

In conclusion, a profile based on a combination of few behavioural symptoms and simple neuropsychological tests that focus on attention, could potentially contribute to a better selection of patients that will unequivocally benefit from treatment with CEIs.

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