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SHORT COMMUNICATION

Accelerated clinical decline in well-educated patients with frontotemporal lobar degenerations

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Abstract Education seems to protect against symptoms of neurodegeneration, but highly educated individuals experience faster cognitive decline after the onset of dementia. No studies on the effects of education on the clinical course in frontotemporal lobar degenerations (FTLD) exist. The aim of the study was to explore the effect of education on the rate of clinical deterioration in patients with FTLD. Thirty-five patients with FTLD were recruited and followed up for 20 months in average. A correlation was calculated between years of education and monthly rate of change on the clinical dementia rating scale sum of the boxes (CDR-SOB). A linear regression analysis with the CDR-SOB monthly rate of change as dependent, and the educational years and other variables possibly associated with the rate of clinical decline as independent variables was performed. There was a significant positive association between education and CDR-SOB monthly rate of change, indicating a faster decline in the well-educated. Education was the only significant predictor of clinical deterioration.

Keywords Frontotemporal lobar degeneration · Frontotemporal dementia · Semantic dementia · Non-fluent progressive aphasia · Cognitive reserve · Brain reserve · Education · CDR · Clinical progression

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Introduction

A growing body of evidence suggests that higher education is associated with cognitive reserve (CR) against the clinical manifestations of neurodegeneration [38], such as in Alzheimer's disease (AD) [32], and frontotemporal lobar degenerations (FTLD) [30, 31]. Possibly less healthy lifestyles of less-educated individuals do not sufficiently explain this phenomenon [29], since it has been observed in populations with a fairly homogeneous lifestyle [27]. Bennett et al. [2] reported that the association between AD pathology and cognitive symptoms shortly before death was attenuated by schooling. Higher educated patients had more plaques than would have been predicted from their cognitive status. Hence, CR had somehow helped to offset brain damage in some individuals. Moreover, several studies indicate that well-educated non-demented elderly individuals experience slower cognitive decline before reaching the state of dementia than the less-educated subjects [43]. In these cases, CR helps to tolerate more brain damage before symptoms of dementia arise. After this threshold is passed, the level of symptoms catches up with the severity of the neurodegeneration. At that stage, symptom progression may be more rapid in well-educated individuals [39].

FTLD is a relatively rare cause of dementia, with a prevalence of 2 in 100,000 persons [35]; however, it is the second most common pre-senile cause for neurodegenerative dementia [14]. It comprises the behavioral variant frontotemporal dementia (FTD), and the two language variants semantic dementia (SD) and non-fluent progressive aphasia (NFPA). The present study was designed to demonstrate that the educational attainment is associated with faster clinical deterioration in FTLD. We hypothesized that higher formal education would be correlated with

an accelerated clinical worsening, consistent with the concept of CR. We furthermore expected that education would be an independent predictor of clinical disease progression, taking into account other variables either associated with clinical decline or CR.

Methods

Subjects

Thirty-five patients with mild to moderate FTLD, including 22 with FTD, five with SD, and eight with NFPA, were recruited at the Center for Cognitive Disorders of the Department of Psychiatry and Psychotherapy of the Technische Universität München. All clinical evaluations were performed by the same psychiatrist (J.D.-S.) between 2003 and 2005. The diagnosis was established according to revised Lund–Manchester criteria [28] by consensus of two psychiatrist with profound experience in the field of FTLD (J.D.-S. and A.K.). All consecutive patients that fulfilled inclusion criteria were selected for the present study. The diagnosis was based on the information from a thorough neurological and psychiatric examination, informant interview, routine blood sampling, MRI, and ^{18}F-FDG PET imaging. The neuropsychological examination by an experienced psychometrician was based on the German version of the Consortium to Establish a Registry for AD assessment battery [42], incorporating the mini-mental-state examination (MMSE) [11]. Executive and frontal tests were also administered (Frontal Assessment Battery (FAB) [9], frontal behavioral inventory (FBI) [16], trail making test (TMT) [36]). Neuropsychiatric symptoms were rated on the neuropsychiatric inventory (NPI) [5], and impaired everyday functioning was assessed using the Bayer activities of daily living (B-ADL) scale [15]. The neuropsychological assessment was carried out by an experienced psychometrician (C.P.). Severity of dementia was rated using the German version of the CDR. The CDR sum of the boxes (CDR-SOB) was used to rate disease progression in this study, because it allows for a more subtle grading of change. The follow-up visit was based on a telephone interview in all patients. Information was gathered from the same proxy as at baseline, a spouse, or child in most cases. The documentation also contained information on the patient's age, gender, age at the onset of symptoms, and years of formal education. At the initial evaluation, three patients were treated with a selective serotonin-reuptake inhibitor (SSRI), four with an antipsychotic, five with a cholinesterase inhibitor, and four with memantine. Two patients were on an SSRI and an antipsychotic, one on an SSRI and a cholinesterase inhibitor, two on an SSRI and memantine, and two on a cholinesterase inhibitor and memantine. Twelve patients did not take any antidementive, antidepressant, or antipsychotic medication. Informed consent according to the Declaration of Helsinki was available for each patient. The study protocol was approved by the local ethics committee.

Statistical analysis

All statistical analyses were carried out in the Statistical Package for Social Sciences (SPSS), v16.0 (SPSS Inc., Chicago, IL, USA). All *P* values given are unadjusted, two-sided and subject to a significance level of 5%. Patient characteristics are given in Table 1. The primary objective of the present study was to relate the duration of formal education to the rate of clinical worsening over time, which was measured as change on the CDR-SOB. A monthly rate of change was calculated according to the following formula:

$$\frac{\text{Follow-up CDR-SOB minus baseline CDR-SOB}}{\text{Months between baseline and follow-up visits}}.$$

A non-parametric correlation (Spearman's rank correlation coefficient) was calculated between the CDR-SOB monthly rate of change and the years of formal education. This analysis was carried out for the entire sample of patients with FTLD and, in a subsequent identical analysis, restricted to the subsample with FTD. The results of the correlation analyses were visualized in a scatterplot and a regression line was fitted into the plot. A one-way ANOVA analysis was performed in order to detect significant differences in the SCR-SOB monthly rate of change between the three diagnostic subgroups. In order to explore the effects of other variables possibly associated with the rate of clinical worsening, such as gender, present age, age at the onset of symptoms, diagnostic category within FTLD, baseline MMSE score, baseline B-ADL score, and baseline CDR-SOB, these variables were entered as independent variables along with the years of formal education in a linear regression analysis, using the CDR-SOB monthly rate of change as the dependent variable. Both a forward and a backward stepwise variable selection were applied. Further non-parametric correlations were performed in an exploratory fashion to explore potentially important associations in the study sample. Corrections for multiple comparisons were therefore not applied. In detail, correlations were conducted between the baseline CDR-SOB score and the years of education in order to explore if patients differed in their baseline disease severity as a function of their educational background. Correlations were also calculated between the years of education as well as the baseline CDR-SOB and all other variables used as predictors in the regression analysis (gender, present age,

Table 1 Patient characteristics

Characteristic	Value
Age	65.29 (9.58)
Age at onset	61.00 (9.27)
Years of education	13.00 (3.65)
FTD:SD:NFPA	22:5:8
Men:women	25:10
CDR-SOB at baseline	5.90 (4.35)
CDR-SOB at follow-up	11.33 (4.78)
Time between baseline and follow-up (months)	19.86 (5.70)
CDR-SOB change between baseline and follow-up	5.43 (3.73)
CDR-SOB monthly rate of change	0.29 (0.22)
MMSE	22.00 (6.15)
CERAD-NAB	
Verbal fluency	7.86 (3.89)
BNT	11.36 (3.71)
Word list learning	12.40 (5.22)
Word list recall	3.08 (2.38)
Constructional praxis	9.76 (1.88)
NPI total score	18.36 (11.30)
FBI total score	24.09 (10.52)
B-ADL total score	5.09 (2.30)
FAB	11.78 (4.33)
TMT A (s)	96.22 (51.87)

Mean (standard deviation) where appropriate; values given for the baseline evaluation, except if indicated otherwise

FTD frontotemporal dementia, *SD* semantic dementia, *NFPA* non-fluent progressive aphasia; *CDR-SOB* clinical dementia rating sum of the boxes (range 0–18 higher values indicating worse clinical status), *MMSE* mini-mental state examination (0–30 higher values indicating better cognitive performance), *CERAD-NAB* Consortium to establish a registry for Alzheimer's disease neuropsychological assessment battery; verbal fluency (animals) 0-not limited, higher values indicating better verbal performance, *BNT* modified 15-item Boston naming test, 0–15 higher values indicating better naming performance, word list learning 0–30, higher values indicating better performance, word list recall 0–10 higher values indicating better performance, Constructional praxis 0–11 higher values indicating better performance, *NPI* neuropsychiatric inventory (0–120 higher scores indicating more severe neuropsychiatric symptoms), *FBI* frontal behavioral inventory (0–72 higher values indicating more severe symptoms), *B-ADL* Bayer activities of daily living scale (0–10 higher scores indicating worse every day performance), *FAB* frontal assessment battery (0–18 higher values indicating better performance), *TMT A* trail making test A (0–240 s higher values indicating worse performance)

age at the onset of symptoms, diagnostic category within FTLD, baseline MMSE score, and baseline B-ADL score).

Results

There were no significant correlations between the years of education and the baseline CDR-SOB as well as the other predictor variables (education $r = -0.07$, $P = 0.68$, $N = 35$). The baseline CDR-SOB was negatively correlated with the MMSE score ($r = -0.47$, $P < 0.001$, $N = 35$), and positively with the B-ADL score ($r = 0.61$, $P = < 0.001$, $N = 35$). The mean monthly rate of change was 0.3 in both the entire FTLD and the FTD samples. There was a significant positive correlation between the CDR-SOB monthly rate of change and the years of formal education ($r = 0.38$, $r^2 = 0.14$, $P = 0.02$, $N = 35$). This correlation remained significant after a restriction of the analysis to the subsample with FTD ($r = 0.37$, $r^2 = 0.13$, $P = 0.05$, $N = 22$); the CDR monthly rate of change did not significantly differ between the three diagnostic subgroups ($P = 0.87$, $F = 0.14$, $N = 35$) (Fig. 1). The regression lines have a positive slope. In the linear regression analysis with the CDR-SOB monthly rate of change as the dependent variable, only the years of formal education entered the model with a forward stepwise variable selection as a significant predictor ($P < 0.01$, $T = 3.37$, $N = 35$). The other independent variables did not exert statistically significant effects (gender $P = 0.18$, $T = 1.31$, $N = 35$, baseline CDR-SOB $P = 0.21$, $T = 1.29$, $N = 35$, diagnosis within FTLD $P = 0.99$, $T = -0.17$, $N = 35$, age $P = 0.55$, $T = -0.53$, $N = 35$, age at onset $P = 0.48$, $T = 0.64$, $N = 35$, baseline MMSE score $P = 0.19$, $T = 1.32$, $N = 35$, baseline B-ADL total score $P = 0.16$, $T = 1.35$, $N = 35$). Applying a backward variable selection did not significantly alter these results.

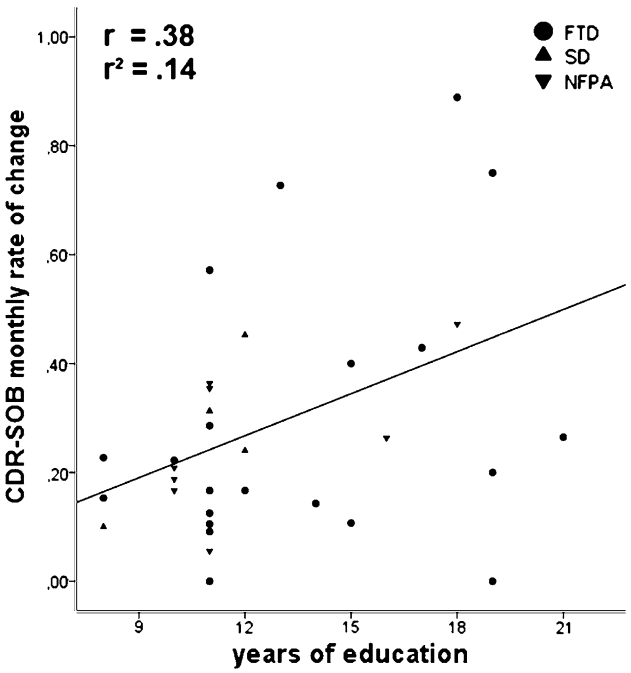

Fig. 1 Scatterplot between education and CDR-SOB monthly rate of change in the entire sample with FTLD; patients of different diagnostic subgroups are marked differently according to the legend

Discussion

This is the first study to explore the association between education and the clinical course of FTLD. We report a significant positive correlation between the length of formal education and the rate of clinical disease progression. This suggests that well-educated patients with FTLD experienced higher rates of clinical deterioration. We furthermore report that only the educational attainment was a significant predictor of accelerated disease progression in a statistical model including other known risk factors for a faster clinical worsening. Patients with FTD, SD, and NFPA were pooled for the present study, which facilitates the generalization to the population with FTLD. However, differences in education and rates of clinical deterioration between the three diagnostic subgroups are unlikely to have affected the results, as a restriction of the analyses to the FTD subgroup did not significantly alter the results. The findings of the present study are in line with the previous reports on the impact of education on the clinical course of AD. Teri et al. [41] reported that the decline of cognitive function became more rapid as AD progressed, and that higher education, younger age, and agitation were also significantly related to increased rates of cognitive decline. Stern et al. [39] confirmed the finding of an increased rate of cognitive decline in well-educated patients with AD.

Some limitations of our study have to be considered. Patients were recruited at a specialized memory clinic; their characteristics might therefore not entirely resemble the entire population with FTLD. Our patients had furthermore rather high levels of education; the effects of education on clinical worsening might be different in less-educated individuals. In addition, most patients with NFPA and SD were in the lower educational range in the present study. Previous studies suggest that the language variants of FTLD show a slower clinical progression [3]. Therefore, other factors than education may have also influenced the progression rate in this subgroup of patients. Moreover, the CDR is a widely used and reliable rating scale for dementia staging in AD, which correlates with autopsy [13] and in vivo findings [33] of neurodegenerative pathology. However, certain behavioral aspects of FTLD, which also determine clinical disease severity, might not entirely be covered by the CDR, and it might also not be the most sensitive instrument for clinical change. However, it has been previously used to stage severity in FTLD [8, 18, 37], it is correlated to neuropathological changes [4] in this particular disorder, and validation studies for the German version [34] and its application via telephone are available [12]. Furthermore, the CDR-SOB was used and a monthly rate of change was calculated that allowed a subtle graduation, and most other instruments were out of the question because the disease staging was performed in a telephone interview at follow-up. Another possible confound is the use of antidementive, antidepressant, and antipsychotic medication, which may have influenced the clinical disease course. The influence of these drugs on behavioral and cognitive symptoms as well as disease progression has not been well-established in FTLD so far. Most evidence stems from case reports or non-controlled and non-randomized studies including small numbers of patients and the results are sometimes contradictory. Most studies are based on the theoretical concepts of serotonergic and dopaminergic deficiencies; however, drugs with other neurotransmitter profiles such as cholinesterase inhibitors and NMDA antagonists have also been studied. In more detail, SSRI including sertraline, and paroxetine showed positive effects on behavioral symptoms in two reports [1, 24]. However, Deakin [6] reported no improvement of behavioral symptoms and worsening of cognition under paroxetin in a randomized controlled study. Trazodone, an SSRI with marked sedative properties, resulted in a significant improvement of some behavioral symptoms, with no effects on cognition [21, 22]. Moreover, antipsychotic drugs including olanzapine [26] and aripiprazole [10] showed some beneficial effects on behavioral symptoms. Last, antidementive drugs including the cholinesterase inhibitors galantamine [17], and donepezil [23], and the NMDA receptor antagonist memantine [7, 40] showed no effects, whereas the cholinesterase inhibitor rivastigmine was associated with an improvement of behavioral symptoms [25]. These results suggest that most evaluated medication options do not show significant treatment effects in FTLD and that effects are rather small if present. However, modifying effects of the clinical disease course cannot be entirely excluded; therefore, inter-individual differences in medication intake may have biased our results. It is, however, unlikely that medication intake was biased towards the less-educated patients, and, therefore, any putative modifying effect would be equally distributed across the entire sample.

Our results provide the first piece of evidence for the role of education in the prediction of clinical disease progression in FTLD. The findings underpin the concept of CR, which predicts that more brain damage is needed to cause symptoms in individuals with high CR. However, once a critical threshold is passed, the effects of neurodegeneration outweigh those of CR and the rate of clinical deterioration increases. Further studies are warranted that investigate if the innate degree of CR can be modified by education, e.g. mediated by adult neurogenesis [19, 20].

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