Are behaviour and motor performances of rheumatoid arthritis patients influenced by subclinical cognitive impairments ? A clinical and neuroimaging study

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Abstract

Objective

To determine whether some behavioural manifestations and poor motor performances in patients affected by rheumatoid arthritis (RA) are due to subclinical cognitive defects.

Methods

We performed a psychometric assessment of 30 patients affected by RA exploring several cognitive domains such as memory, visual-spatial integration, motor planning, mental flexibility, relating performances with morphological and functional neuroimaging (MRI and SPECT). We also related the cognitive data with the Ritchie and Lee indexes and other clinical parameters.

Results

We found an impairment in visual-spatial tasks in 71% of patients with a high correlation to activity and disease severity as expressed by the Ritchie and Lee indexes ($p < 0.005$; $p < 0.01$). Furthermore, we detected in 38% of patients some difficulties in mental flexibility related to the Lee Index ($p < 0.05$). These poor performances are related to hypoperfusion of the frontal and parietal lobes as detected by brain SPECT; this finding is more evident in patients with brain white matter alterations on MRI.

Conclusions

Our data allow us to hypothesize that manual dexterity could be due to a disconnection between subcortical white matter and parietal-frontal lobes because of microangiopathy; furthermore, a chronic reduction in sensorial stimuli by impaired joints could lead to produce an alteration in motor planning cognitive processes.

Key words

Rheumatoid arthritis, cognitive impairment, neuroimaging.

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Introduction

In recent years there has been increasing interest in the role of the central nervous system (CNS) in determining disability in rheumatic diseases (1). The loss of physical and emotional skills in daily living assumes a social relevance in rheumatoid arthritis (RA): the chronic-progressive evolution of pain and morning stiffness is often associated with a deterioration in psychological well-being leading to an impaired quality of life. It is accepted that in the course of RA the decrease in the psychological status of patients follows the experience of the illness, resulting from chronic distress and deterioration in one's functional abilities, which reduces the ability to cope with the disease (2).

In systemic erythemathosis lupus (SLE) cognitive impairment is frequently detected which co-occurs with emotional disturbances, contributing to the development of disability (3, 4). In particular, the impairment of non-verbal skills and executive functions have been described in more than 25% of SLE patients, while only a few contradictory findings have been produced about other rheumatological diseases (5). We can argue that such neurological involvement could affect RA patients as well.

In clinical practice, the neurological assessment of patients affected by rheumatic diseases is infrequent and is usually reserved for patients with clear signs of a brain lesion. The new techniques of brain imaging (MRI, PET, SPECT) have a high sensitivity to structural and functional changes in the brain, but cannot detect the subtle modifications in neural pathways which could cause a wide range of behavioural phenomena. On the other hand, neuropsychological assessment can provide a useful approach for evaluating and monitoring brain activity; furthermore, in some conditions - for example in traumatic brain injury, it may provide evidence of CNS dysfunction independent of results obtained using neuroradiological techniques (5).

Given the present lack of data, the CNS involvement in RA should be investigated both to define the presence of subclinical conditions influencing the main features of the disease and to verify the role of cognitive performance in coping with disability.

We performed this cross-sectional study on a sample of patients affected by RA to test the following hypotheses: (1) Are there subtle cognitive deficits in patients with RA ? (2) Are there clinical correlations between the severity of the disease and cognitive impairments? (3) Is a correlation between brain imaging features and cognitive deficits detectable ?

Patients and methods

A total of 30 RA patients diagnosed following the ARA criteria (6) (3 males, 27 females) with a mean age of 55.6 ± 11.1 (range 32-71) were recruited. Inclusion criteria were: i) duration of disease > 1 yr, ii) onset of disease >16 yrs of age, iii) activity of disease requiring pharmacological treatment, iv) educational level > 3 years, v) absence of psychiatric or neurological diseases in the clinical hystory, vi) no current treatment with CNS drugs, and vii) no present history of depression.

Disease activity was evaluated based on the number of swollen joints (Score 0-42), the Ritchie articular index (Score 0-78), early morning joint stiffness (EMS) in minutes, together with the erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). The severity of disease was established following the Lee functional index.

Since some neuropsychological tests require hand-skills, we performed a structured assessment of manual dexterity to exclude those patients with severe motor impairment due to chronic joint inflammation. We used the Frenchay Arm Test (7) because of its reproducibility, its validity and its representation of the daily habits of included subjects, fixing a cut-off score of < 12/25.

In order to exclude the presence of low brain perfusion due to cervical spine or atlantoaxial joint rheumatoid alterations, we employed the following diagnostic algorithm: each patient had lateral radiographic views taken with the neck in flexion and extension. If this latter examination was negative, the

patient underwent cerebral MRI and SPECT directly. If rheumatoid involvement of the atlantoaxial joint was documented, the patient underwent cervical spine MRI, brain MRI with angiographic scanning, and transcranial Doppler ultrasonography (TCD).

Finally, using the Beck Depression Inventory we excluded patients with mood disorders. The neuropsychological assessment was performed by two trained neurologists in two different sessions lasting 60 minutes each - one for each patient; the assessments took place at the same time of the day (before lunch, nearly 3 hours after taking medication) to avoid problems of stiffness and pain which could influence the execution of cognitive tasks.

The cognitive assessment (comprising attention, memory, visual-spatial and executive abilities) was performed using the following tests.

Attention Matrices Test

This is a cancellation task to test sustained and focal attention. In it the patient is asked to cross out target digits randomly distributed among many others on a sheet; the task increases in difficulty in 3 trials: firstly, the target is just one digit (i.e. number 5), then two digits (i.e. numbers 2, 6) and finally 3 digits (i.e. numbers 1, 4, 9). For each trial 45 seconds are allowed. The final score is given by the global amount of targets crossed-out (maximum score is 60).

Trail Making Test A and B (TMT A and B)

This test consists of two parts both of which must be performed as soon as possible. In part A a series of randomly distributed numbers on the page from 1 to 25 must be connected in ascending order. In part B the patient must alternate between numbers and letters while connecting them in ascending order (e.g. 1A- 2B - 3C etc.). The score is represented by the time used. These tests explore divided attention and mental flexibility.

Verbal Fluency

We explored this function using two different modalities. In verbal fluency for categories, patients are requested to say as many words as possible in a specific category (animals, cities, fruits and colours) in one minute for each category; the final score is represented by the total numbers of words. The second modality involved phonemic cueing. Patients have to say as many words as possible beginning with a specific letter (A,F,S): in this task 1 minute for each letter was allowed and then a computation of all the words was carried out. These two tasks explore the ability to generate words and depend on frontal lobe function. The distinction between the semantic and phonemic approaches is useful to detect specific semantic deficits.

Wisconsin Card Sorting Test (WCST)

This is considered a classic frontal test which allows the assessment of mental flexibility and the ability to shift from one task to another by learning through one's own errors. In this test the patient is asked to classify 128 cards containing 3 different items in a logical order following a rule which is established by the rater but not communicated, so that each patient has to discover the general rule by performing different trials and receiving feed-back from the rater. There are 3 different categories (classification for colour, shape and number of items) that can be repeated. The final score reflects how many times each patient has discovered the rule (maximum 6).

Progressive Coloured Matrices of Raven

In this test the patient is asked to choose the best match between a target stimulus and 6 different options. It is useful for assessing abstract reasoning abilities and is considered not to be influenced by the educational level of the subject. There are 36 items and the final score is the total of correct answers (maximum 36).

Block Design

This is a subtest on the Wechsler Adult Intelligence Scale (WAIS) which explores visual-spatial abilities. The patient is requested to arrange in order some coloured blocks to obtain a shape which is suggested by the rater. This test has 2 levels of increasing difficulty: first the patient uses 4 blocks for 5 easier items and 60 seconds are allowed; the patient is then given 9 blocks for 5 more complex shapes and 120 seconds are allowed. Each item has its own score based on the time employed to perform it. At the end all scores are globally computed (maximum 48).

Rey Figure (B)

This complex figure is used to assess the ability to reproduce a copy of a visual stimulus and remember it after 15 minutes. The final score depends on how many details are reported after the delay.

Rey Word List

This test is employed to assess verbal learning abilities. Each patient is asked to learn a list of 15 different words which is presented five times. The final score, which represents the efficiency of verbal long-term memory, is based on the number of recalled words after 15 minutes.

Luria Motor Trials

This motor task assesses motor-planning abilities and reflects frontal lobe function. It involves 3 different series of simple, complex and reversed movements which must be performed by hand, separately. The score for each trial is 0 when patients commit 3 or more mistakes; it is 1 for two mistakes, and 2 for just one mistake; the score is 3 when patients commit no errors (maximum 18).

Beck Depression Inventory (BDI)

This is largely used in psychometric investigations for mood assessment and includes 22 questions with four options for each one, scaled for severity: the higher the score, the more depressed the patient is (maximum 63) (8). We used as the cut-off for depression a score of 11, which means at least 50% of the items are scored O.

Cerebral MRI scans were taken using a Siemens Scan at 1.5 Tesla. SPECT scans were performed with a gamma-camera GCA-602 Toshiba, using 20 mCi of ^{99m}Tc-ECD (ethylene cystine

dimer) injected 30 minutes before the scan at rest and without visual or acoustic stimuli. Data collection was performed using 6 steps, each lasting 30 seconds with a total of 60 frames and slices of 1 cm by filtered back projection.

All SPECT scan interpretations were performed by visual analysis by the same rater, who was blind to the clinical status of patient. Likewise, we were not able to use a scoring system for MRI scans, so the interpretation was subjective.

Data analysis

We considered patients as "impaired" in a specific cognitive task following this method: for some tests (TMT A and B, Raven, Attention Matrices, Verbal Fluency) we adopted the Equivalent Score which is based on a transformation of the raw score into a level of performance tailored to education and age: the range is from 0 to 4, where 0 = definitely impaired and 1 = moderately impaired, respectively (Italian Normative Data) (9). We considered patients "impaired" when their equivalent score was 0 or 1.

For the Rey Figure and Rey Word List we used the available normative data (10); we then performed a normalization of the raw scores, considering as pathologic more than two standard deviations from the normal mean score. For the Block Design test we adopted as the cut-off point a score lower than 24; this corresponds to the maximum achievable in the first 6 items, which are the less complex. We adopted this method after observing the mean performances of people of that age and education level routinely assessed in our laboratory. For the WCST Italian normative data are not available: we therefore considered as the cut-off point less than 2 correct performances in the card classification. Likewise, for the Luria Motor Trials, we considered as the lower limit a score less than 12/18, which means at least 30% mistakes in all the tasks globally considered.

We correlated the cognitive findings with the Ritchie and Lee indexes and the other clinical parameters using the Mann-Withney test; furthermore, we used Multiple Regression Analysis to evaluate the influence of each clinical parameter in performance. Clinical correlations were not corrected for multiple comparisons.

Results

We examined 47 in-patients consecutively referred to the Institute of Internal Medicine of the University of Ancona: 17 of these (mean age 59 years and 5 years of disease) were excluded because they were depressed according to the above cut-off score at BDI. The clinical characteristics of the examined series are shown in Table I. Patient medications were: NSAIDs in 10 subjects, cyclosporine + NSAIDS in 2 subjects, cyclosporine + methotrexate in 10 subjects, Ccyclosporine + steroids in 5 subjects, and steroids + NSAIDs in 3 subjects.

An abnormal prevalence of impaired cognitive performances in RA patients was detected, particularly in attentional tasks, planning abilities and cognitive flexibility (Table II): only 2 patients performed in the normal range on all tasks. The neuropsychological assessment showed an impairment of attention in RA patients. In particular, the sustained attention (TMT A) score was below the normal range in 38% of patients: this finding was related to the duration but not to the severity or activity of the disease as expressed by the Ritchie and Lee Indexes, respectively. Impaired divided attention (TMT B) was also evident in 38% of patients, showing a correlation with the Lee index ($p < 0.05$).

Table I. Demographic and clinical characteristics of patients (mean scores and standard deviation).

Mean age	55.6 ± 11.1
Mean education	5.78 ± 2.5
N° of swollen joints	19.1 ± 10.8
N° of tender joints	24.9 ± 14.0
Early morning stiffness (minutes)	83.8 ± 38.6
Esr	57.9 ± 36.1
Crp	4.1 ± 4.6
Ritchie index	17.5 ± 8.1
Lee index	14.5 ± 7.7
Disease duration (years)	11.8 ± 10.8

At the same time, in 71% of patients we found a defective performance in tests exploring visuo-spatial and planning abilities (Block-Design): this finding was related to the Ritchie and Lee Indexes ($p < 0.005$ and $p < 0.01$, respectively). Furthermore, 47% of patients showed a poor performance in WCST which explores cognitive flexibility, with a correlation to the Lee Index ($P < 0.05$) but not with the duration or activity of the disease. For phonemic verbal fluency also there was a trend to impaired performance (43% of subjects), in contrast to semantic verbal fluency (6%), although it was not related to the other clinical parameters. With regard to memory we found a dichotomy: visual memory (Rey figure) was impaired in 50% of subjects but without any correlation to clinical parameters. On the other hand the slighter impairment in verbal memory (Rey word list)

Table II. Rate of impaired performances at psychometric assessment and their correlation-with clinical parameters (for more details see methods). Correlation with clinical parameters (Mann-Whitney test).

Test	Rate of impaired	Ritchie	Lee	Duration Disease	Swollen Joints	Esr	Crp	Ems
Attention matrices	12%	Ns	Ns	Ns	Ns	Ns	Ns	Ns
Trail making test a	38%	Ns	Ns	0.03	Ns	Ns	Ns	Ns
Trail making test b	38%	Ns	0.05	Ns	Ns	Ns	Ns	Ns
Semantic verbal fluency	6%	Ns	Ns	Ns	Ns	Ns	Ns	Ns
Phonemic verbal fluency (afs)	44%	Ns	Ns	Ns	Ns	Ns	Ns	Ns
Block design	71%	0.005	0.01	Ns	0.03	Ns	Ns	Ns
Winsconsin card sorting test	47%	Ns	0.05	Ns	Ns	Ns	Ns	Ns
luria motor trials	29%	Ns	Ns	Ns	Ns	Ns	Ns	Ns
rey figure	50%	Ns	Ns	Ns	Ns	Ns	Ns	Ns
rey word list	35%	Ns	Ns	Ns	Ns	Ns	Ns	Ns
progressive coloured matrices raven	0	Ns	Ns	Ns	Ns	Ns	Ns	Ns

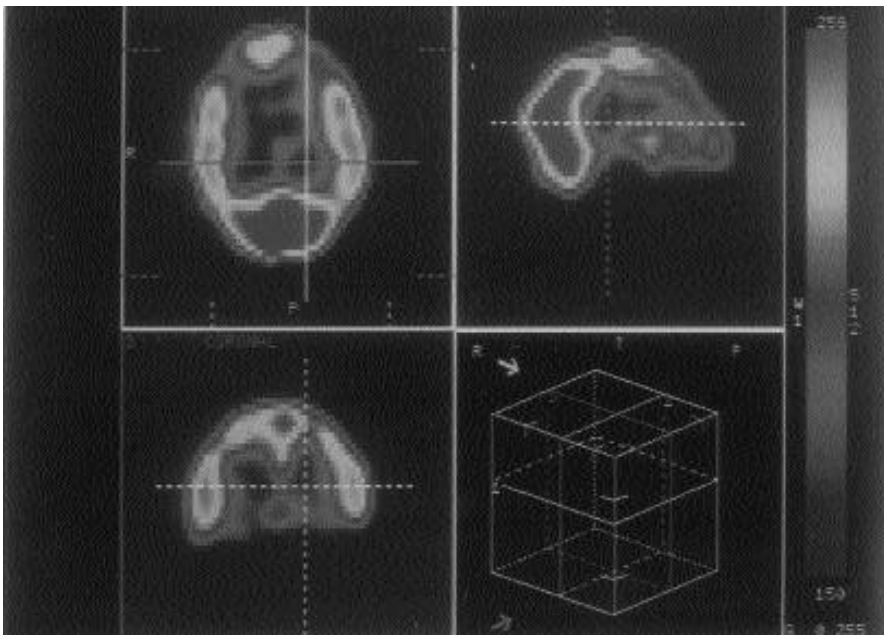

Fig. 1. Typical cerebral SPECT scan of a patient with attentional, executive and visuo-spatial disorders: note the hypoperfusion of the frontal (more evident) and right parietal lobe.

was related to the Ritchie index.

A failure in sequential motor planning (Luria trials) was detected in almost one-third of patients (29%) but without any correlation to the duration or severity of disease. As for the other clinical parameters, we found significant correlation between the number of swollen joints with the Block Design ($p < 0.003$) only; no correlation between ESR, CRP, EMS and psychometric measures was found.

On Multiple Regression Analysis, where age, education, duration of disease, and the Ritchie and Lee indexes were taken as independent variables and cognitive scores as dependent variables, we found an effect of age on WCST only ($p = 0.01$). No relationship was ascertained between age and the other cognitive tasks. On the contrary, the influence of the Ritchie and Lee indexes on executive function (Block Design, Phonemic Verbal Fluency, WCST) was confirmed.

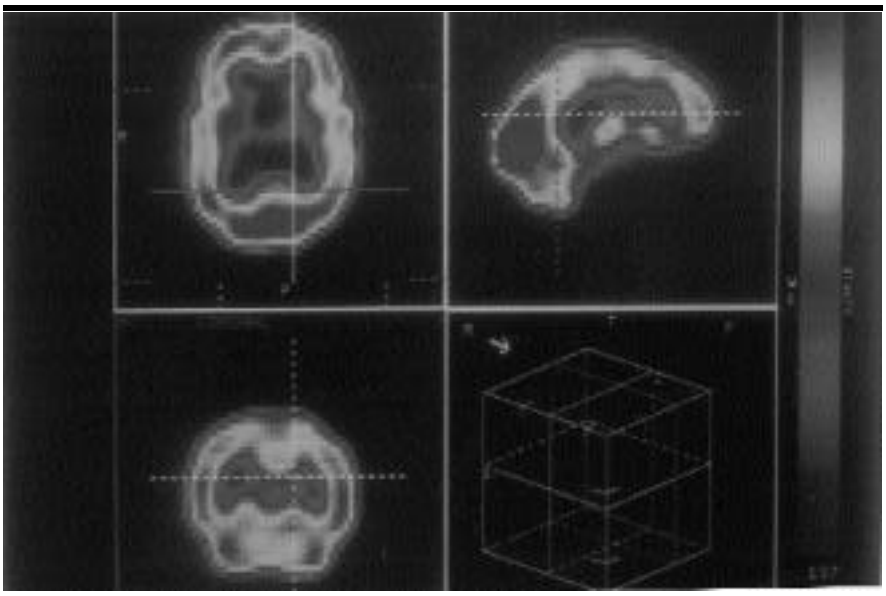

Fig. 2. Cerebral SPECT scan of a patient with normal performances in all psychometric tests:note the normal perfusion of the whole brain.

MRI imaging showed in 35% of patients (11 out of 30) some alterations at the subcortical level in terms of white matter hyperintensities (WMHIs) without leukoaraiosis: all of these patients had low scores in the attentional, executive and visuo-spatial tests. Furthermore, 85% of the patients (26 out of 30) showed at SPECT hypoperfusion of the frontal lobes with an associated involvement of the parietal lobes in 40% (14 out of 30) (Figs. 1, 2).

Discussion

CNS involvement in the course of RA is considered to be an infrequent event (6), and there are conflicting results in a few surveys regarding the occurrence of cognitive or behavioural abnormalities (5). Hanly for example (11), studied SLE and RA patients with a one year follow-up and concluded that cognitive disfunction is evanescent. However, in that study only 44% of RA patients underwent a repeat evaluation and, furthermore, there was no functional neuroimaging data. We know that neuropsychological assessment is quite sensitive to the presence of subclinical CNS dysfunction when no structural lesions are clinically evident (5) and brain imaging studies do not address the different behavioural features of an altered neural substrate: therefore it is relevant to detect a correlation between neuropsychological and imaging data.

We hypothesized that to some extent the emotional disturbances and behavioural manifestations observed in RA and usually considered to be a reaction to the loss of skill and competencies could also be due to a direct expression of an altered neural substrate. In this regard it could be supposed that subtle brain involvement in patients with RA can contribute to a lack of initiative and an impaired perception and elaboration of external stimuli which, together with the joint stiffness and pain, enhances the development of the disability.

As far as we know no previous studies have assessed RA patients correlating neuropsychological and instrumental

data to clinical parameters. According to Carbotte (5), cognitive-functional assessment in the course of connective tissue disorders can detect subtle involvement of the CNS at an early stage, before any brain lesion appears on CT or MRI. Furthermore, in several pathological conditions, such as HIV encephalopathy, the onset of the disease can show neuropsychological aspects in 10 - 30% of subjects (12). In this study, we selected neuropsychological tests according to the clinical data of previous surveys on SLE (13-15) and on their widely demonstrated sensitivity to brain dysfunction (16).

Interestingly, the cognitive functional profile in our study was related to the severity but not to the duration of the disease, with the exception of sustained attention. The neuropsychological results are related to the location of hypoperfusion revealed by SPECT imaging, which showed a selective involvement related to the quoted cognitive defects. This finding leads us to hypothesize that RA may cause a slow, but progressive subclinical dysfunction of some cortical areas of the brain. It could be argued that parietal hypoperfusion on SPECT is somewhat unexpected and that some of these patients might have underlying Alzheimer's disease (17). However, there is some evidence that the chronic use of antiflogistic medications, as in RA, has a protective role against dementia (18); therefore, we think that our results are likely due to RA and not to early dementia. Lastly, Multiple Regression Analysis confirmed the substantial influence of disease severity on executive functions independently of age, with the exception of WCST. Visual analysis of scans is open to subjective interpretation and represents a limitation of our investigation. Furthermore, subcortical white matter abnormalities on MRI were detected in one-third of patients and this pattern was not related to their age.

Several different hypotheses can be formulated about the mechanism determining these cognitive defects in RA. Firstly, a disconnection between cortical and subcortical areas due to vasculitis located at the small penetrating arterioles can be postulated, considering that vasculitis is the most important pathogenic event for the involvement of different organs in RA, i.e. skin ulcers or peripheral neuropathies (19). This condition may explain both the hypoperfusion, as detected by SPECT (see photos), and WMHIs at MRI.

According to Hachinski (20), some cognitive alterations (e.g. attentional and executive disorders) that do not characterize full-blown dementia because of their selectivity could be due to small infarcts of cortical-subcortical pathways secondary to small arteriole damage. Furthermore, some authors stress the fact that a minimal loss of cerebral tissue at strategic locations can cause cognitive impairment in patients with vascular disease (21-23). Such a pathogenic condition must be distinguished from the diffuse cerebral angiitis detectable by neuroimaging and may be more similar in appearance to the slight vascular damage common in elderly (24, 25).

A further hypothesis that may explain the cognitive impairment in RA is related to deafferentation: a defective propioceptive input to the brain from joints altered by inflammation and chronic damage could cause an impairment in the cognitive mechanisms of elaboration and planning motor activity. In fact, motor skills are related to the ability of the brain to plan movements: recent f-MRI studies showed the role of parietal lobes in the sequence of voluntary movements (26), while frontal lobes play a crucial role in monitoring their execution. With regard to this, the functional imaging (SPECT) of our survey showed cerebral hypoactivity in the parietal and frontal lobes in a large number of patients. Therefore, the poor motor performance and lack of skill displayed by them could be due to articular impairment followed by a prolonged reduction of inputs to the cerebral cortex: other studies (27, 28) demonstred that brain activation during motor tasks may include a substantial component related directly to the processing of afferent sensory information. Our hypothesis seems to be confirmed by the close relationship between cognitive motor planning defects and RA in terms of chronically severe disease, and not in terms of active inflammation.

We must point out two limits to the present study. The first concerns the diagnosis of depression, since we relied on the Beck Depression Inventory which is actually a self-assessment tool. However, each patient also underwent a preliminary interview with one of the authors (M.B.), who has clinical experience in neuropsychology, in order to evaluate those symptoms (e.g. fatigue, dysphoria) and non-verbal features (e.g. mimic, eyes contact) of depression which may not be detected by the above test.

The second limit was the lack of control group: we preferred to use normative data as our reference because of the difficulty in finding volounteers without diseases such as hypertension or diabetes, which are very common in middle-aged people and may potentially cause cognitive impairment due to microangiopathy.

The educational level of the patients included in this study was not high, but is is almost representative of mean level of Italian people over 50 years.

In conclusion, our results suggest a possible CNS involvement in RA patients: these findings should be considered from both a diagnostic and a therapeutic point of view, in order to plan an early specific treatment able to limit the neurobehavioural impairments which may hamper the patient in coping with increasing disability. Further studies are desirable to co nfirm our data.

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