Cognitive and psychosocial features in childhood and juvenile MS: Two-year follow-up
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Cognitive and psychosocial features in childhood and juvenile MS
Two-year follow-up

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ABSTRACT

Objective: To assess the evolution of cognitive and psychosocial functioning in a cohort of childhood and juvenile multiple sclerosis (MS) cases after a mean period of 2 years had elapsed since baseline evaluation.

Methods: In this cohort study, we used the same extensive neuropsychological battery with alternative versions of the tests assessing memory, attention/concentration, executive functions, and language. Fatigue and depression were also measured. An interview on school and daily living activities was obtained from the parents. The cognitive performance of the patients was compared with that of demographically matched healthy controls (HC).

Results: Fifty-six patients and 50 HC were assessed. At follow-up, criteria for cognitive impairment (failure on at least 3 tests) were fulfilled in 39 patients (70%) and 75% of the cases were classified as having a deteriorating cognitive performance. Changes were prominent in tests of verbal memory, complex attention, verbal fluency, and receptive language. In the regression analysis, the only significant predictor of cognitive deterioration was older age of the subject (odds ratio 1.9, 95% confidence interval 1.2–2.9, p = 0.003). Psychiatric disorders, most frequently depression, were diagnosed in 12 patients (30.5%). Fatigue was reported by 21% of the patients. MS negatively affected school and everyday activities in 30% to 40% of the subjects.

Conclusions: Our findings confirm the importance of systematic assessment of cognitive and psychosocial issues in children and teens with MS. The progressive nature of the cognitive difficulties emphasizes the need for developing effective treatment strategies. Neurology. 2010;75:1134–1140

GLOSSARY
CCI = cognitive change index; CDI = Children Depression Inventory; DMD = disease-modifying drug; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; HC = healthy controls; MCST = Modified Card Sorting Test; MS = multiple sclerosis; SDMT = Symbol Digit Modalities Test; SPART = Spatial Recall Test; SPART-D = Spatial Recall Test-Delayed; SRT = Selective Reminding Test; SRT-D = Selective Reminding Test-Delayed; TMT = Trail Making Test; TOL = Tower of London.

The high prevalence and functional impact of cognitive impairment are well-documented in adult-onset cases of multiple sclerosis (MS). Comparatively little is known about the impact on cognitive and psychosocial functioning of MS in children and adolescents, who represent 3%–5% of all MS cases. Recent studies reported cognitive dysfunction in approximately one-third of these patients, with a negative impact on school and everyday activities. There is, however, no information on the evolution of these deficits over time, which is of critical importance for helping children and adolescents deal with disease-related challenges.

In a previous multicenter study, we assessed cognitive and psychosocial functioning in a cohort of 63 childhood and juvenile MS cases, compared with a group of healthy controls (HC). We found a 31% prevalence of cognitive impairment and a low IQ in 28% of the cases. As compared with adult-onset cases, the neuropsychological pattern was peculiar due to the presence of language problems in 20%–40% of the cases. Extrapolation of these findings
predicts a high functional impact, since skills involving cognitive faculties are increasingly emphasized in the future academic career of these patients.

In this follow-up study, we reassessed cognitive and psychosocial functioning in the same cohort of patients after a mean period of 2 years to evaluate the evolution of the cognitive deficits, impact on school and everyday activities, and relationships with demographic and clinical variables.

**METHODS Subjects.** The original study cohort included all the childhood and juvenile MS cases referred to 11 Italian MS Centers between January 2006 and June 2007. Fifty-six out of 61 patients of the original cohort were reassessed after a mean period of 2.1 ± 0.4 years. At the moment of evaluation, all the cases were relapse-free and had not taken steroids for at least 30 days. Due to the unavailability of subjects recruited in the baseline assessment, an entirely new group of 50 demographically matched HC was recruited among the patients’ friends and schoolmates and assessed at the coordinating center in Florence. The HC had no neurologic or major psychiatric illness, history of learning disabilities, serious head trauma, alcohol or drug abuse, or major medical illnesses.

**Standard protocol approvals, registrations, and patient consents.** The parents and participants provided written informed consent. The study was approved by the ethical standards committee of the University of Florence.

**Clinical and neuropsychological assessment.** In each center, the patients were followed up prospectively, undergoing clinical examination every 6 months and at the time of a relapse. Information including treatments, relapses, and disability on the Expanded Disability Status Scale (EDSS) was recorded by the neurologists over the follow-up period. The same trained psychologist participating in the baseline assessment administered the neuropsychological test battery to patients and controls and a structured interview to the patients’ parents. As in the baseline assessment, cognitive impairment was defined as failure on at least 3 tests. Failure of a test was defined as a score under the 5th or over the 95th percentile of the HC performance. We calculated an individual cognitive change index (CCI) to provide precise indication of the amount and direction of change in cognition over the follow-up period (see below).

The neuropsychological test battery was the same as in the baseline assessment, including alternative versions of the tests. For the absence of alternative versions, the Modified Card Sorting Test (MCST) was replaced by the Tower of London Test. The following cognitive areas were assessed:

- Verbal learning and delayed recall through the Selective Reminding Test (SRT), Selective Reminding Test-Delayed (SRT-D) from Rao’s battery.
- Visuospatial learning through the Spatial Recall Test (SPART), Spatial Recall Test–Delayed (SPART-D) from Rao’s battery.
- Complex attention through the Symbol Digit Modalities Test (SDMT) from Rao’s battery and the Trail Making Test (TMT A and TMT B).
- Planning through the Tower of London Test (TOL). The TOL was presented under the form of 2 identical kits (initial and target configuration) made of a wooden base (22 × 6 × 2 cm) with 3 rods of 12 cm, 8 cm, and 4.5 cm and 3 balls (yellow, red, and blue) of 3 cm in diameter. The subject was required to produce the target configuration in a minimum number of moves; move only 1 ball at a time; place at most 1 ball on the shortest peg and 2 balls on the middle one; and move each ball only from one peg to another. There were no time limits. The execution time and the number of moves were measured by the examiner. The results (target configuration attained or not, abandoned) and any rule violations were noted.
- Expressive language through a semantic and phonemic verbal fluency test and an oral denomination test from the Aachener Aphasie Test.

Depression was self-assessed using the Children Depression Inventory (CDI). At follow-up, we also used the kiddie-SADS, Present and Lifetime Version diagnostic interview. This is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria. It is administered by interviewing the parents and child and it allows the examiner to achieve summary ratings including all sources of information. Objective criteria are provided to rate individual symptoms.

Fatigue was self-evaluated by cases and HC through the Fatigue Severity Scale (FSS).

As at baseline, the psychologist administered the parents of the patients a structured 15-item interview, gathering information on school activities, hobbies, sports, and family and social relationships in the previous year.

The neuropsychological test battery was administered in a single session. Breaks were provided on subject request or when fatigue was evident. The whole assessment required from 2 hours to 2.5 hours (on average, 70 minutes for the test battery and 80 minutes for other interview issues).

**Statistical analysis.** Group comparisons were performed using the Student t test, Mann-Whitney test, and χ² test, with Bonferroni correction for multiple comparisons.

In order to permit a more appropriate comparison between the patient and control performance, as in the baseline analysis, the study sample was divided into 2 subgroups. The first included subjects aged 10 to 15 years and the second subjects aged more than 15 years. Test scores of each patient were therefore compared with scores obtained from the HC within the appropriate subgroup. The mean and SD for each test variable was derived from the matched control data. To calculate the individual CCI, for each test, 0 was assigned if a patient scored at or above the control mean. Grade 1 was assigned if a patient scored below the control mean but within 1 SD of that mean. If the patient scored at least 1 but not more than 2 SDs below the control mean, they were allocated a grade 2. This procedure was repeated until all patient scores were graded. The grades were summed across all neuropsychological variables to give one overall measurement of cognitive dysfunction for each patient on the 2 assessments. Finally, we calculated the change on the cognitive impairment index for each participant between year 0 and year 2. A variation of at least 2 points on the CCI identified patients with improving or deteriorating cognitive performances. Demographic and clinical predictors of cognitive changes were assessed through stepwise regression logistic models. All statistical analyses were performed using SPSS software, version 12.2, running on Windows (SPSS, Chicago, IL, 2002).
RESULTS  The study sample consisted of 56 patients with MS and 50 demographically matched HC (table 1). At the second evaluation, the mean EDSS score of the patients had increased slightly up to 1.7. Forty-eight (88%) cases were treated with disease-modifying drugs (DMD), 41 with interferon-β, 2 with glatiramer acetate, 1 with azathioprine, and 3 with natalizumab (mean treatment duration 2.7 ± 2.3 years, range 0.2–10.0 years). Mean latency between clinical onset and the beginning of therapy was 3.3 ± 3.9 years (range 0.1–15.9 years).

Cognitive findings. Mean scores of the cases and HC are listed in table 2. Using Bonferroni correction, the mean scores of the patients were significantly lower on all the verbal memory tests, on the TMT-A, on the verbal fluency test, on the semantic stimulus, and on 2 out of the 3 verbal memory tests. Moreover, 39 cases (70%) failed at least 3 tests and were classified as cognitively impaired, as compared with 31% at baseline. Thirteen cases (22.6%) exhibited minor degrees of cognitive dysfunction, failing 2 tests. The proportion of cognitively impaired patients was 57% in subjects aged <15 years and 70% in those aged >15 years (p = 0.4). As at baseline assessment, mean IQ score of patients classified as cognitively impaired was lower than that of patients classified as cognitively preserved (90.3 ± 20.7 vs 113.4 ± 11.1, p < 0.001).

The proportion of patients failing each test tended to increase for most of the variables, with the exception of the Indication of Pictures Test. Tests more frequently failed by cognitively impaired subjects tapped verbal learning and delayed recall, verbal fluency, verbal comprehension, and complex attention (table 3). The profile of the deficits was comparable in the 2 age subgroups, with the exception of the semantic fluency test, which was more frequently failed by patients aged ≥15 years (p = 0.022).

Table 4 shows the proportion of patients classified as stable, improving, and deteriorating at the follow-up assessment using the CCI. We also repeated the analysis after excluding the patients with an IQ score <90. In this analysis, 17 (50%) out of 34 cases were classified as cognitively impaired and 26 (76.5%) as deteriorating on the basis of the CCI.

Using Bonferroni correction, the comparison between cases classified as improving/stable (25%) and those classified as deteriorating (75%) revealed a poorer cognitive outcome in subjects with an older age (p < 0.001) and higher educational level (p < 0.001), whereas there was not any difference in terms of gender, MS duration, age at MS onset, cognitive impairment at baseline, EDSS score, mean number of interim relapses, DMT, mean CDI and FSS scores, or IQ score (p > 0.05) (table 5).

In a regression analysis including all the above-mentioned variables, only older age (1.9 odds ratio, 95% confidence interval 1.2–2.9, p = 0.003) was confirmed to be a predictor of deteriorating cognitive performance.

Psychosocial findings. The Kiddie-SADS Psychiatric Interview was obtained in 39 cases and documented psychiatric disorders in 12 cases (30.5%): the diagnosis was major depression in 6 subjects, depression and anxiety in 2, panic disorders in 2, and bipolar disorders in 2. The psychiatric diagnoses were already known and the cases were being followed up by a psychiatrist. All but one were classified as cognitively impaired. Excluding these subjects from the analysis on cognitive functioning, 63.6% of the cases was classified as impaired at the second evaluation and 73.8% as deteriorating on the basis of the CCI.

Depressive symptoms on the CDI were reported by 9 out of 53 cases (17%), as compared with 6% at baseline.

Using a cutoff score of 4 on the FSS, based on the fifth percentile of HC scores, fatigue was reported by 11 (21%) of the patients.

An interview with the parents was obtained in 39 cases (25 classified as cognitively impaired): from the mother in 35 and from the father in the remaining cases. The interviews revealed that school activities and achievements were negatively affected in 11 cases (28%). Four patients had a support teacher and 7 patients had to repeat a year in school. A high number of school days had been missed (≥30 days) in 90% of the patients due to medical appointments, relapses, and therapy side effects. Hobbies and sports

### Table 1 Characteristics of the study sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n = 56)</th>
<th>Controls (n = 50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>28/28</td>
<td>28/22</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y, mean ± SD; range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (10–15 y)</td>
<td>12.5 ± 1.3; 10.9–14.4</td>
<td>11.2 ± 1.8; 8.9–14.6</td>
<td>NS</td>
</tr>
<tr>
<td>Group 2 (≥15 y)</td>
<td>17.9 ± 1.8; 15.0–20.6</td>
<td>18.6 ± 2.4; 15.1–20.8</td>
<td>NS</td>
</tr>
<tr>
<td>Education, y, mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (10–15 y)</td>
<td>5.9 ± 2.0; 3–8</td>
<td>4.8 ± 8.6; 3–8</td>
<td>NS</td>
</tr>
<tr>
<td>Group 2 (≥15 y)</td>
<td>11.4 ± 1.9; 8–14</td>
<td>11.4 ± 2.5; 8–14</td>
<td>NS</td>
</tr>
<tr>
<td>Age at onset, y, mean ± SD; range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.7 ± 3.8; 1.3–17.4</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Disease course</td>
<td>Relapsing-remitting</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>EDSS score, mean ± SD; range</td>
<td>1.7 ± 1.0; 0–5.5</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>MS duration, y, mean ± SD; range</td>
<td>5.5 ± 3.7; 1.4–17.4</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>No. of relapses in the last year, mean ± SD; range</td>
<td>0.6 ± 0.7; 0–3</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>No. of relapses in the last 2 y, mean ± SD; range</td>
<td>1.0 ± 1.3; 0–5</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NS = not significant.
were also negatively impacted in 16 patients (41%), with 8 patients reducing or changing their usual sport activities and 8 quitting sport activities altogether. Finally, family and social relationships were negatively affected in 11 cases (28%).

**DISCUSSION** There is increasing correlative evidence from experimental animal studies and functional imaging studies that white matter changes can play a critical role in cognitive and psychiatric disorders. For instance, myelination of appropriate brain regions appears to coincide with the development of specific cognitive functions. Moreover, the degree of myelination correlates with normal cognitive development, IQ, and normal variation in a few cognitive skills, including aspects of language. Children and adolescents with MS may therefore be particularly vulnerable to cognitive problems, since the neuropathologic processes of the disease occur during primary CNS myelination and can produce both white matter and gray matter changes. On the other hand, it is also believed that brain plasticity and ability of recovery may be more efficient in this age range, which might counterbalance the impact of CNS damage and mitigate its consequences.

To date, information on cognitive issues from longitudinal studies is extremely limited. In a previous study, 12 participants were evaluated with a brief neuropsychological test battery on 2 occasions, with a mean follow-up of 21.58 months. Most patients experienced some cognitive deterioration over time and only the baseline disability level was correlated with changes in cognition.

In this study, we reassessed a cohort of 56 children and adolescents after 2 years. The dropout rate was 8.8%. At follow-up assessment, 70% of the cases fulfilled our criterion for significant cognitive impairment, whereas another 22% exhibited minor degrees of cognitive dysfunction. As at baseline...
cance level was a disease-modifying drug; EDSS
Abbreviations: CCI Scale; MS Measured at baseline on the Wechsler Intelligence Scale for Children–Revised.

Table 5  Characteristics of patients with MS with deteriorating and stable/improving cognitive performance on the basis of the CCI

<table>
<thead>
<tr>
<th></th>
<th>Deteriorating (n = 39)</th>
<th>Stable/Improving (n = 13)</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>16/23</td>
<td>10/3</td>
<td>0.025</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>18.0 ± 1.7</td>
<td>14.9 ± 2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education, y, mean ± SD</td>
<td>11.5 ± 2.0</td>
<td>8.5 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at MS onset, y, mean ± SD</td>
<td>12.7 ± 3.3</td>
<td>10.5 ± 3.1</td>
<td>0.045</td>
</tr>
<tr>
<td>MS duration, y, mean ± SD</td>
<td>5.4 ± 3.6</td>
<td>4.4 ± 1.9</td>
<td>0.226</td>
</tr>
<tr>
<td>EDSS score, mean ± SD</td>
<td>1.5 ± 0.7</td>
<td>1.5 ± 1.1</td>
<td>0.998</td>
</tr>
<tr>
<td>No. of relapses in last year, mean ± SD</td>
<td>0.5 ± 0.6</td>
<td>0.9 ± 1.0</td>
<td>0.187</td>
</tr>
<tr>
<td>No. of relapses in last 2 y, mean ± SD</td>
<td>1.0 ± 1.2</td>
<td>1.2 ± 1.7</td>
<td>0.664</td>
</tr>
<tr>
<td>Cognitively impaired at baseline, n (%)</td>
<td>8 (20.5)</td>
<td>6 (46.2)</td>
<td>0.071</td>
</tr>
<tr>
<td>Treated with DMDs, n (%)</td>
<td>33 (84.6)</td>
<td>11 (84.6)</td>
<td>0.999</td>
</tr>
<tr>
<td>Mean CDI score, mean ± SD</td>
<td>10.1 ± 7.8</td>
<td>11.5 ± 8.9</td>
<td>0.612</td>
</tr>
<tr>
<td>Mean FSS score, mean ± SD</td>
<td>3.0 ± 1.3</td>
<td>3.1 ± 1.1</td>
<td>0.755</td>
</tr>
<tr>
<td>Total IQ, mean ± SD(^b)</td>
<td>99.3 ± 19.8</td>
<td>97.5 ± 20.8</td>
<td>0.791</td>
</tr>
</tbody>
</table>

Abbreviations: CCI = cognitive change index; CDI = Children Depression Inventory; DMD = disease-modifying drug; EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; MS = multiple sclerosis.
\(^a\) Student \( t \) test, \( \chi^2 \) test, and Mann-Whitney test used when appropriate. Statistical significance level was \( p < 0.004 \) after Bonferroni correction.
\(^b\) Measured at baseline on the Wechsler Intelligence Scale for Children–Revised.

assessment, mean IQ score of patients classified as cognitively impaired was significantly lower than that of patients classified as cognitively preserved.

These findings point to further cognitive decline over time, or decline from previously normal functioning occurring in the majority of the cases. Consistent with this, the individual CCI showed a deteriorating test performance in 75% of the cases. It should be noted that, since in this follow-up study we had a completely new control group, the expected learning effect that might be seen in the controls might have underscored the differences between the 2 groups.

This follow-up study suggests a worse cognitive outcome in children and adolescents compared with adults. In fact, longitudinal studies in adults have shown a heterogeneous cognitive outcome, with progression of the deficits in the longer term and stability in a few patients for substantial periods of time.26,27 In our cohort, the deterioration involved the majority of the cognitive measures, in particular those tapping verbal memory, complex attention, verbal fluency, and receptive language. Deterioration in language skills confirms that the profile of deficits in this age range may be different compared to adult-onset cases, where linguistic abilities are usually preserved.

As for predictors of cognitive deterioration, multivariate analysis showed that only older age was associated with a worse cognitive outcome.

We can hypothesize that patients with MS, particularly those aged ≥15 years, who are in a critical phase for development of cognitive and academic competences, are more likely to show a gap in cognitive test performance when compared with healthy peers who in the same period are attaining cognitive abilities at a very fast rate. Hopefully, this gap might be mitigated over time due to compensatory and therapeutic strategies. Only long-term longitudinal studies have the potential of elucidating the definitive cognitive outcome of the patients and the time-dependent nature of relationships with demographic and clinical variables.

Another possible explanation of cognitive worsening is the higher inflammatory activity documented in this age range compared with adult cases.28 Indeed, in our sample, although the difference was not significant, patients aged ≥15 years compared with the younger group exhibited a higher mean number of interim relapses (1.1 ± 1.4 vs 0.6 ± 0.8, \( p = 0.17 \)). On the other hand, EDSS scores, MS duration, proportion of DMD treatment, and treatment delay from disease onset were strictly comparable between the 2 age groups. Also, in this follow-up assessment, we found that most of the clinical variables were not relevant to the subject’s cognitive status. Our findings are in agreement with reports on cognitive impairment in adults which have shown poor or inconsistent relationships with disability levels and disease duration.22,29-32 MRI studies have shown more consistent and robust correlations with several MRI parameters dealing with both white and gray matter changes.3 An MRI analysis of imaging correlates of cognitive functioning is currently ongoing in a subgroup of participants, which may reveal more meaningful clinico-pathologic associations.

While there is preliminary evidence of a possible beneficial effect of DMD therapy on cognitive functioning, we did not find any significant impact from DMD treatment on the cognitive performance of our cases. Although most of our patients were under treatment, only 14 subjects were treated within 1 year from disease onset. It is possible that earlier treatment may positively influence the cognitive outcome of subjects in the long term.33

Fatigue is one of the most frequent and invalidating symptoms in adult patients with MS.34 In our study, we used the FSS and applied a cutoff score of 4 on the basis of the HC assessment. With this approach, we documented significant fatigue in 21% of the cases. It is possible that the FSS is not fully adequate to capture symptoms in a pediatric population and that some items may require adaptation or modification. Alternatively, different and more specific assessment tools should be validated and used. Depression is another
highly prevalent disturbance in MS and one of the most important determinants of patients’ quality of life. In children and adolescents, self-assessment on the CDI may have low sensitivity. In fact, using the Kiddie-SADS interview, we found a 47% prevalence of psychiatric disorders, represented by major depression in half of the cases. The frequent occurrence of psychiatric problems in this age range clearly deserves further research and calls for regular screening and treatment in clinical practice.

Finally, we confirmed that the disease had great functional impact and that, beyond the extent of physical disability, cognitive problems play a relevant role, negatively affecting school, everyday, and social activities.

On the whole, our findings emphasize the importance of systematic assessment of cognitive and psychosocial issues to provide prompt management and counseling. The progressive nature of the cognitive difficulties suggests that the development of effective rehabilitative strategies tailored to the needs of these young patients is a priority for future research in the field.

AUTHOR CONTRIBUTIONS
Statistical analysis was conducted by Dr. Emilio Portaccio.

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DISCLOSURE
Dr. Amato has served on scientific advisory boards for Biogen Idec, Bayer Schering Pharma, and Sanofi-Aventis and receives research support and speaker honoraria from Biogen Idec, Merck Serono, Bayer Schering Pharma, and Sanofi-Aventis. Dr. Goretti reports no disclosures. Dr. Ghezzi has served on scientific advisory boards for Merck Serono and Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Bayer Schering Pharma, Biogen-Dompé AG, Merck Serono, and Novartis; has served as a consultant for Bayer Schering Pharma, Sanofi-Aventis, and Teva Pharmaceutical Industries Ltd.; has received speaker honoraria and funding for travel from Biogen Dompé AG, Merck Serono, Bayer Schering Pharma, and Novartis; and has received research support from Merck Serono and Novartis.

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