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Cognitive impairment in pediatric multiple sclerosis

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Abstract Cognitive impairment has been recently recognized in patients with pediatric multiple sclerosis in more than 30% of cases. Altered functions with variable frequency are: attention, language (receptive, verbal fluency, naming), visual-spatial and motor functions, spatial memory, executive functions and abstract reasoning. Fatigue and affective disorders are associated, but not correlated with cognitive impairment. The frequency and severity of cognitive impairment increase with time. Cognitive impairment has a negative impact on patient's life limiting social, academic and recreational activities.

Keywords Cognitive impairment · Childhood · Adolescence · Multiple sclerosis

Introduction

Cognitive impairment (CI) occurs in about 40–60% of adult multiple sclerosis (A-MS) patients; it is not exceptional at the onset of the disease, and increases over time (Amato MP, present volume). The finding that CI can also affect subjects with pediatric MS (Ped-MS) is relatively recent. The aim of this study is to summarize literature data on this topic, and to discuss the psychosocial implications of CI in Ped-MS.

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The frequency and severity of CI in children and adolescents with MS

The first cohort of patients systematically investigated with a neuropsychological battery included ten children with MS [1]. Tests were administered to evaluate general intelligence, receptive and expressive language, attention, visual memory, academic functioning, and executive functioning. It was found that all children failed on at least one test, with some children showing deficits in most or all areas. The deficit was more severe in children who were younger at MS diagnosis, and who had a longer disease duration. The severity of MS was low, suggesting that CI is independent of physical disability.

Attention, language, memory, visual-spatial and motor functions were tested in a cohort of 37 patients with a mean age of 14.8 years and a mean EDSS of 1.5 [2]. A total of 13 patients (35%) showed CI, defined by impaired performance on at least two tests. Using the less restrictive criterion of failure to only one test, 22 patients showed a mild CI (59%). Attention was impaired in 29.7% of subjects, language was also frequently affected, with impairment in naming in 18.9% of cases and poor receptive language in 13.5%; delayed recall was impaired in 18.9% of patients. Affective disorders were diagnosed in six patients. CI correlated to EDSS, number of relapses, age at onset, disease length.

The occurrence of CI in Ped-MS has been further investigated in a cohort of 63 Ped-MS patients, who were compared with 57 demographic-matched healthy controls [3]. The following cognitive areas were tested: global cognitive functioning (IQ), verbal learning and delayed recall, visuospatial learning and delayed recall, sustained attention, abstract reasoning, expressive language, and receptive language. Five patients with MS onset before 10 years (8%) exhibited a IQ <70, and 17 (28%) scored between 70 and 89.

Criteria for significant CI (failure in at least 3 tests) were fulfilled in 19 patients, whereas 32 patients (53%) failed at least two tests. The frequency and type of tests failed by cognitively impaired patients is reported in Fig. 1. CI was predicted by IQ level, and was not related with age, gender, relapses in the previous 1–2 years, EDSS, fatigue, and depression. As for general intelligence, lower IQ score was predicted by younger age at onset.

A subsequent analysis was performed in this cohort, to identify the tests with the highest discriminant ability for detection of CI [4]. The administration of the Selective Reminding Test, the Symbol Digit Modalities Test, the Trail Making Test, and the Vocabulary Test from the Wechsler Intelligence Scale for Children yielded a sensitivity of 96% and a specificity of 76%. These tests are suggested as a screening tool for a brief neuropsychological battery for children.

Follow up studies

Studies in adults with MS have shown that CI tends to deteriorate with time. This issue has also been confirmed in children; 12 ped-MS cases were re-tested 11–30 months after the basal assessment (mean follow-up duration 21.6 ± 9.3) [5]. The frequency at which patients performed in the impaired range increased on several tasks, with Trail Making Test showing the largest increase in impairment frequency. An association was found between the number of tests failed and baseline EDSS ($r = -0.58$); the association was slight and not significant with relapses.

Almost all patients of the Italian cohort (56 of 63) were re-examined about 2 years after the first assessment [6]. The whole disease duration was 5.3 ± 3.7 years, and the mean EDSS score was 1.7 ± 1.0. In spite of a short interval after the initial assessment, a short disease duration and a low level of physical disability, the percentage of cases with significant CI increased to 70%. Thirteen patients (22.6%) showed a mild CI, and only four patients (7%) remained cognitively preserved at the end of follow-up.

Psychosocial issues

CI is associated with limitations in social, academic and recreational activities. MS-related school absences and assistance to school activities have been reported in 10% [3] and 35% [2] of cases. Some patients had to repeat the year in school because of missed school days or cognitive difficulties. Minimal (struggling but obtaining passing grades) to severe (unable to function in regular classroom) school difficulties were observed in 29% of 137 children with MS [7]. Hobbies and sport activities are also negatively affected; it was observed in 34% cohort of the Italian [3].

Fatigue and affective disorders can coexist with CI, and contribute to impair social activities. Affective disorders were diagnosed in 6 of 13 children who underwent a structured psychiatric evaluation (major depression and anxiety disorder-not otherwise specified in two, two major depression, anxiety not otherwise specified in one, panic disorder and generalized anxiety disorder in one) [2]. The

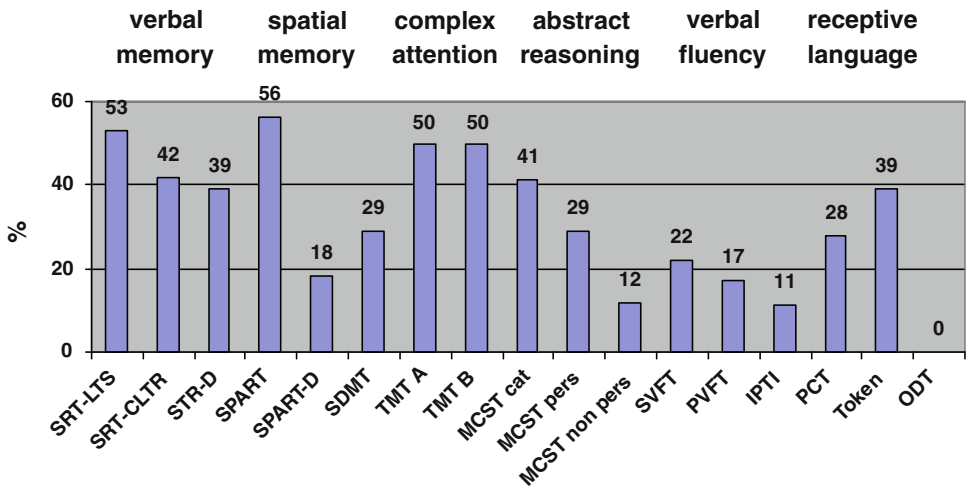

Fig. 1 Frequency and type of tests failed by cognitively impaired patients, according to Amato et al. [3] *SRT-LTS* Selective Reminding Test-Long Term Storage; *SRT-CLTR* Selective Reminding Test-Consistent Long Term Retrieval; *SPART* 10/36 Spatial Recall Test; *SDMT* Symbol Digit Modalities Test; *TMT-A/B* Trail Making Test A/B; *SRT-D* Selective Reminding Test-Delayed; *SPART-D* 10/36 Spatial Recall Test-Delayed; *MCST cat* Modified Card Sorting Test completed corrected categories; *MCST pers* Modified Card Sorting Test perseverative errors; *MCST non-pers* Modified Card Sorting Test non-perseverative errors; *SVFT* Semantic Verbal Fluency Test; *PVFT* Phonemic Verbal Fluency Test; *IPT* Indication of Pictures Test; *PCT* Phrase Comprehension Test; *Token* Token Test; *ODT* Oral Denomination Test

Table 1 Frequency of self- and parent-reported difficulties with fatigue and quality of life variable, according to MacAllister et al. [9]

	Fatigue	Sleep	Cognition	Physical	Emotional	Social	Academic
Self-report severe (%)	32	11	26	20	10	4	28
Parent-report severe (%)	51	36	42	10	10	8	14

rate of depression was lower in the Italian cohort (6%); data were further analyzed including the Kiddie-SADS-Lifetime Version-PL semi-structured interview, showing an increased frequency of cases with affective disorders: major depression was found in 15%, depression and anxiety in 5%, panic disorders in 5%, bipolar disorders in 5% of 39 children. [8].

Fatigue was found in 9 of 63 cases with a cut-off score of four in Fatigue Severity Scale, as proposed for adults, but in 46 (73%) using a cut-off score of two, corresponding to the fifth percentile of healthy controls [3]. Fatigue was diagnosed in 18/37 patients (48%) in another study [2]. Behavioral changes were reported by parents in 39% of cases of the Italian cohort [3].

Fatigue and quality of life have been recently investigated in a study including 51 ped-MS patients, who were examined with self- and parent-report scales [9]. Fatigue was assessed by means of PedsQL Multidimensional Fatigue Scale, that includes scales to measure fatigue, sleep disturbances, cognitive fatigue; quality of life was assessed via the pedsQL scales, providing measures of physical, emotional, social, and school functioning. EDSS was the only variable associated to fatigue and QoL. The frequency of severe difficulties with fatigue and quality of life is reported in Table 1. Fatigue correlated with sleep difficulties, cognitive problems and QoL variables.

Conclusion

To summarize, CI occurs in a high proportion of cases with Ped-MS, increasing in frequency and severity after a short-term follow up. Altered functions with variable frequency are: attention, language (receptive, verbal fluency, naming), visual-spatial and motor functions, spatial memory, executive functions and abstract reasoning [1–3]. Fatigue and affective disorders are associated, but not correlated with CI.

Due to the crucial role of myelin in optimizing mechanism of learning and information processing [10], demyelinating lesions during CNS maturation in pathways involved in cognition are an important cause of CI. Visuo-spatial memory, attention, executive functions, language are strongly involved in cognitive and academic performances, affecting activities such as listening to lengthy instructions, organization of unstructured assignments, generation of novel ideas, efficient processing speed, organization of cognitive and behavioural strategies [1].

Cognitive dysfunction during biological and psychological development is likely to involve an impairment of cognitive structures necessary for future acquisitions of academic achievements and cognitive strategies. The occurrence of a functional deficit in addition to a structural damage is suggested by MRI data, showing that brain damage is less severe and the capability to compensate damage is greater in pediatric than in adult MS patients [11–13]. This finding is also suggested by clinical studies showing that Ped-MS has a less severe physical impairment as compared to A-MS with a similar disease duration, as Ped-MS patients reach moderate or severe disability after a longer interval, about 10 years later [14]. It is possible that children and adolescents activate compensatory mechanisms limiting the extent of CI during the long-term evolution of the disease: to verify this issue that it will be important to have long-term data on IQ of Ped-MS patients.

Conflict of interest None.

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