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VISUOSPATIAL SKILLS AND ANTISEIZURE MEDICATIONS IN CHILDREN

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ABSTRACT — Aim: The aim of this study was to investigate visuospatial abilities in children and adolescents with different types of epilepsy treated with antiseizure monotherapy.
Methods: A neuropsychological assessment was performed at baseline and after one year. 207 subjects diagnosed with epilepsy and pharmacologically treated with monotherapy including levetiracetam, ethosuximide, valproic acid, carbamazepine or oxcarbazepine and 45 controls were recruited and were compared by gender and age. To evaluate visuospatial perception and memory we used Rey-Osterrieth Complex Figure. All subjects performed the test at baseline and after 12 month of drug therapy. For the statistical analyzes we regarded: age at onset of epilepsy, epilepsy type, seizure frequency, side and lobe of seizure onset, ASM dose, epilepsy duration, non-verbal intelligence, age, sex, executive functions. EEG, seizure frequency, and drug dose were also recorded.
Results: Subjects with epilepsy executed only in the Immediate Recall test significantly worse than controls at baseline. There are no differences between clinical groups. We observed a correlation between Instant Recall scores and executive functions, age of seizure onset and epilepsy duration. There was a significantly worsened re-evaluation in the mean score to Immediate Recall in the valproic acid, ethosuximide and carbamazepine groups while no change was noticed in the levetiracetam and oxcarbazepine group.
Conclusion: A visuospatial memory deficit may be present in children with epilepsy compared to control, and this deficit may be related to some aspects of epilepsy and to executive functions; visuospatial memory should be monitored in pediatric subjects which can be influenced by some drugs used for the treatment of seizures.

KEYWORDS — epilepsy, visuospatial memory, antiseizure drugs, children.

INTRODUCTION

Perception skills and visuospatial memory are indispensable cognitive domains for each individual (Burlea et al., 2010; Linn & Petersen, 1986; Sarancha et al., 2021; Vizniuc et al., 2021). Visuospatial perception allows to manipulate non-linguistic symbolic information while visuospatial memory allows to store both visual and spatial information (Aliotti & Rajabiun, 1991, Lupu et al., 2016a, Lupu et al., 2016b). These skills begin to develop very early and are perfected during adolescence (Sorrentino et al., 2019). Some studies in literature show that children and adolescents with epilepsy have an impairment of visual-spatial skills; for example in the study by MacAllister et al. (2019) founded that patients with epilepsy have a significantly lower visual perception index than controls. In general, subjects with epilepsy seem to have deficits in some higher cognitive skills such as executive functions, social perception as well as visuospatial skills. These deficits appear to be associated with other factors such as type of epilepsy, frequency of the seizures and even the drug used to treat the seizures (Dodrill, 2004). Antiepileptic drugs are useful for treating seizures, but they can have a negative effect on a cognitive level as they act on the developing nervous system (Operto et al., 2020a; Operto et al., 2020b). However, newer drugs appear to have little impact or no interference on cognitive functioning, such as levetiracetam or perampanel (Operto et al., 2019; Operto et al., 2020c). The aim of our observational study is to analyze the visuospatial abilities of perception and memory in pediatric and adolescent subjects suffering from different forms of epilepsy treated with pharmacological monotherapy, using standardized tests at baseline and after 12 months of therapy. We also evaluated the incidence of clinical and demographic variables (age at onset of epilepsy, epilepsy type, seizure frequency, side and lobe of seizure onset, ASM dose, epilepsy duration, non-verbal intelligence, age, sex, executive functions) bounded to epilepsy on visuospatial abilities.

RESEARCH METHODOLOGY

Participants — The clinical sample in this study consisted of 207 children and adolescents aged 6 to 18 years old with a new diagnosis of epilepsy recruited at the Child Neuropsychiatry Unit of the University Hospital of Salerno between January 2013 and January 2020. The control group includes 45 healthy subjects homogeneous for age and se recruited during a screening program. The parents of all participants provided written informed consent after receiving a full description about the purpose of the study and about procedures involved.

Assessment — All participants were administered tests to evaluate their non-verbal intelligence abilities (Raven's Progressive Matrices). At baseline Rey-Osterrieth Complex Figure Test (RCFT) was administered to the control group and clinical groups to evaluate visuospatial perceptual and visuospatial memory ability and Epitrack Junior was administered to subjects with epilepsy for assessing executive functions, After 12 months of antiseizures monotheraphy: subjects with epilepsy (n=183) after 12 months performed Rey-Osterrieth Complex Figure Test (RCFT).

Rey-Osterrieth Complex Figure Test (RCFT) — It is a neuropsychological test examine the ability to reproduce a complicated drawing by copying and then drawing from memory recall, it is used to evaluate visuospatial perceptual and visuospatial memory ability in children and adults. The drawings are evaluated following by assigning a score between 0 and 2.

Epitrack Junior — EpiTrack Junior is a screening tool for assessing executive functions, it includes six activities aimed at attention, working memory and executive functions. The age-corrected maximum score is 49 and scores below 32 points indicate a deficit in executive function with different levels of severity.

Statistical Analysis — Scores were expicited as mean ± standard deviation (SD) and the percentage of participants with a score <2 standard deviations was considered. Following the use of the Kolmogorov-Smirnov normality test and after verifying the presence of data not normally distributed, non-parametric tests were used for our analysis. Chi-Square test with Yates correction or Fisher's exact test were used to compare proportions; Kruskal Wallis H test was used to compare mean scores in two independent samples, and Wilcoxon's signed rank test was used to compare mean scores in two related samples. The two-tailed Spearman rank correlation test was used to analyze the relationships between the variables and the correlations were judged as follows: <0.2, low; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, good; 0.81 to 1.00, very good. Statistical Package for Social Science software, version 23.0, was used to analyze the data (IBM Corp, 2015) and our assumptions were analyzed using Bonferroni's adjusted alpha levels of 0.0025 per test (0,05/20).

RESULTS

Clinical and control sample characteristics — 634 medical records were initially considered, but 427 were excluded due to the presence of ASM polypharmacy and other neurodevelopmental disorders. In addition, we retrospectively enrolled 207 children and adolescents with epilepsy aged 6 to 18 years (mean = 10.35 ± 2.39) who performed the Rey-Osterriet Complex Figure Test before and during ASM monotherapy with levetiracetam (n = 58), valproic acid (n = 60), ethosuximide (n = 22), oxcarbazepine (n = 23) or carbamazepine (n = 44). We also recruited a control group consisting of 45 age / sex matched subjects. Subjects in the 5 ASM groups did not differ significantly in demographic or clinical characteristics. After twelve months of treatment with ASM, all subjects in the clinical group had a ≥75% reduction in seizures or were seizure-free. At the one year follow-up, different ASM treatment led to comparable reductions in seizure frequency. The five clinical groups and the control group did not differ significantly in non-verbal IQ, as found by the standard progressive matrices.

Assessmet at baseline — Analyzing the scores obtained on the Rey-Osterrieth Complex Figure Test-Direct Copy test, 6.76% of the subjects with epilepsy showed a score below normal (<5th percentile), while 7.25% had a score at the low limits of normal (5th-15th percentile) while the controls scored 0% a score below normal and 2.23% a score at the low limits of the norm. These differences were not statistically significant on Fisher's exact test. As shown by the Kruskall-Wallis H test for unpaired sample, average of Rey-Osterrieth Complex Figure Test -Direct Copy scores of the five treatment groups (Leviracetam, Valproic Acid, Ethosuximide, Oxcabezepine, and Carbamazepine) and the control group did not differ significantly from each other. The Spearman correlation test showed that, in the total sample of epilepsy patients, Rey-Osterrieth Complex Figure Test -Direct Copy scores were related to age, non-verbal QI and age of onset of epilepsy, instead there is no there was no significant association with the duration of the seizure frequency. Furthermore, no significant difference was found in average scores based on variables of sex, side of onset of seizures and the seizure onset lobe (Kruskall-Wallis test). Evaluating the Rey-Osterrieth Complex Figure Test -Immediate Recall scores we found that 7.25% of the subjects with epilepsy showed a below normal score (<5° percentile), 12.56% of patients showed a score at the low limits of normal (5^{th}–15^{th} percentiles) versus 2.23% and 4.45% of the control subjects respectively. These differences were not statistically significant on Fisher's exact test. In the sample of patients with epilepsy, Rey-Osterrieth Complex Figure Test -Immediate Recall scores were related to age, age of onset of epilepsy and duration of epilepsy, but no meaningful association with non-verbal IQ and seizure frequency was found, as shown by Spearman's cell linking test. Furthermore, no significant difference was found in average scores based on variables of sex, side of onset of seizures and seizure onset lobe (Kruskall-Wallis test).

Evaluation at time 1 and comparison of baseline and time 1 — The re-evaluation was performed only in subjects with epilepsy (n=183) after 12 months. Rey-Osterrieth Complex Figure Test -Direct Copy scores in 9.84% of patients were below normal (<5th percentiles), while 8.20% of patients achieved a score at the low limits of the norm (5^{th}–15^{th} percentiles). On the RCFT-Immediate Recall test 21.74% of subjects with epilepsy scored below normal (<5^{th} percentiles), and 10.14% scored at the low limits of the norm (5^{th}–15^{th} percentiles). We found that the mean Rey-Osterrieth Complex Figure Test -Direct Copy scores were not significantly different from baseline in any of the 5 drug treatment groups. Comparing the mean RCFT-Immediate recall scores we found that in the VPA, ETS and CBZ groups the mean scores were significantly lower at Time 1 compared to baseline, while in the LEV and OXC groups the mean scores did not differ at Time 1 compared to the baseline.

DISCUSSION

There are many elements that contribute to cognitive functioning in children and adolescents with epilepsy (Lagae, 2006). In recent years, the incidence of ASM therapies on cognitive functioning and memory has been highlighted. For this reason, the choice of the type of drug therapy for crisis management must be made with care, especially when it comes to pediatric subjects. In fact, in children, cognitive skills are essential for good adaptability in all contexts of life (Lagae, 2006). The sample from our longitudinal retrospective study consisted of 207 epileptic patients who were introduced to drug monotherapy with levetiracetam, ethosuximide, valproic acid, carbamazepine or oxcarbazepine. All patients underwent a neuropsychological evaluation for visual-spatial perception and memory both before and after twelve months from the introduction of the therapy. In accordance with the previous studies our data showed that subjects with epilepsy had impairment of visuospatial memory skills while the visuospatial perception was preserved. The worst performance in visuospatial memory in our sample was linked to an earlier onset and longer duration of epilepsy and executive functions, while there was no significant association with non-verbal intelligence. The data collected, support the evidence that an early onset of seizures can lead to a worse deterioration of cognitive functions, affect the development of the neuronal system still in development (Kellermann et al., 2015; O'Reilly et al., 2018). In this study there is a positive relationship between visuospatial memory skills and executive functions at baseline, not in visuospatial perception skills. In future studies, the role of executive functions, such as working memory or focused attention, on visuospatial memory could be investigated with a multifactorial analysis. It is possible hypothesize that visuospatial memory is linked to executive functions, which in epileptics may be deficient or impaired by drugs (Operto et al., 2020a). In our sample, at 12 months of re-evaluation, visuospatial perception skills were not significantly different from baseline in the five treatment groups while visuospatial memory skills changed depending on the type of ASM employed. Kruskall-Wallis H test to compare mean scores showed that the mean Rey-Osterrieth Complex Figure Test-Immediate Recall scores of the levetiracetam, ethosuximide, valproic acid, carbamazepine or oxcarbazepine group were not significantly different from each other, but were all significantly lower compared to the control group. In particular, in our study it was found that visuospatial memory is more impaired in children and adolescents taking older ASMs (valproic acid, ethosuximide and carbamazepine) than in newer drugs (levetiracetam and oxcarbazepine). This data agrees with the data already present in the literature (Hessen et al., 2009). In agreement with our results in the literature, a good tolerability to levetiracetam and oxcarbazepine has been shown (Tzitiridou et al., 2005). Furthermore, the study data are in line with another of our previous studies (Operto et al., 2020a). A limitation of our study was the small size of the truck, as well as the use of a retrospective study of a single test to evaluate visuospatial abilities. In addition, no multiple correlation analyzes were performed that took into account multiple neuropsychological variables that could affect performance. In future studies, the role of individual executive functions, such as working memory or focused attention, on visuospatial memory could be investigated with a multifactorial analysis.

CONCLUSION

This study shows that some of the antiepileptic drugs used in pediatric age have a different tolerability on the cognitive profile and in particular on the visuospatial memory abilities after 12 months of treatment. Specifically, valproic acid, ethosuximide and carbamazepine can contribute to a worsening of memory-visuospatial performance, while levetiracetam and oxcarbazepine do not seem to have the same influence on these abilities. Future studies with larger samples and placebo-treated control groups would be useful to confirm these results.

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