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Methylphenidate improves the quality of life of children and adolescents with ADHD and difficult-to-treat epilepsies

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ABSTRACT

Objective: Comorbidity between difficult-to-treat epilepsies and ADHD is frequent and impacts negatively on quality of life. The commonly held (yet poorly substantiated) view that stimulants may worsen seizure control has prevented studies from evaluating the impact of such treatment in this population. Our aim was to study the effect of methylphenidate on the quality of life of children and adolescents with difficult-to-treat epilepsies and comorbid ADHD.

Methods: The study was an open-label, noncontrolled trial with intention-to-treat analysis following 30 patients for 6 months. Subjects received methylphenidate following 3 months of baseline, during which antiepileptic drugs (AEDs) were adjusted and epilepsy, ADHD, and quality-of-life variables were assessed. Multivariate regression analysis identified the main variables correlated with outcome.

Results: Only one patient withdrew because of seizure worsening. Following methylphenidate introduction, doses were titrated up to 0.40–0.50 mg/kg/day. A marked improvement in quality-of-life scores and a significant reduction in seizure frequency and severity were observed. Female sex, reduction of core ADHD symptoms, and tolerability to adequate doses of methylphenidate were significantly associated with improved quality-of-life scores.

Conclusion: These preliminary data suggest that methylphenidate treatment is safe and effective in patients with ADHD and difficult-to-treat epilepsies, positively impacting on quality-of-life scores.

1. Introduction

Epilepsy affects around 1% of children and adolescents [1]. These patients often present behavioral and cognitive symptoms that fulfill DSM-5 criteria for psychiatric disorders [2,3]. In particular, attention-deficit/hyperactivity disorder (ADHD), which affects approximately 5% of children worldwide [4], has been described as a prominent psychiatric comorbidity in epilepsy [5–7].

Current evidence suggests that 12 to 60% of children with epilepsy have ADHD, with higher figures in patients with severe epilepsies [6–9]. The mechanisms underlying the comorbidity are unclear but likely involve genetic factors [10]; frequent seizures, epileptiform discharges, and the effects of antiepileptic drugs (AEDs) may also combine to trigger ADHD symptoms [11,12].

Both conditions have been independently associated with low quality-of-life scores [13–16]. However, ADHD symptoms often appear before seizure onset [17], suggesting that the seizures and their treatment may not have much to do with the psychiatric comorbidity. Hermann et al. [18] reported 23 patients with ADHD and new-onset epilepsy: in 19, ADHD symptoms preceded seizure onset. An epidemiologic study showed that the risk of epilepsy was 2.5 times greater in children who had already developed ADHD symptoms [5].

Attention-deficit/hyperactivity disorder is a chronic disorder which persists into adulthood in about two-thirds of patients and causes a negative impact on familial and social relationships, academic achievement, and occupational status [19]. Treating ADHD is, thus, crucial to improve quality of life for patients and families [20,21]. Although a number of psychosocial interventions have been proposed, the cornerstone of treatment for ADHD is stimulant medication [22]. However, in the presence of comorbid epilepsy, a clinical dilemma ensues because of the long held view that methylphenidate may reduce the seizure threshold and interfere with seizure control [23,24].

Nonetheless, this view has been challenged on several accounts. First, methylphenidate is as effective in alleviating ADHD symptoms in patients who have associated epilepsy as it is in patients with ADHD without epilepsy [20,25,26]. Furthermore, available data do not indicate loss of seizure control with methylphenidate in patients with well-controlled epilepsy [20,27–29], and the limited data suggesting otherwise are not conclusive [30].

While it is well established that children with comorbid ADHD and difficult-to-treat epilepsies face educational, physical, social, and emotional difficulties that directly impact quality of life [13,26], it is

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not known whether treatment of ADHD with stimulants improves quality of life in these patients. In this study, we investigated a sample of patients with difficult-to-treat epilepsies and ADHD seen in a tertiary epilepsy center, treated their ADHD symptoms with methylphenidate, and measured the impact of the treatment on quality-of-life scores.

2. Methods

2.1. Subjects and methods

This was an open-label, noncontrolled trial with intention-to-treat analysis conducted at the Severe and Refractory Epilepsies Outpatient Clinic of the Hospital São Lucas da PUCRS in Porto Alegre, Brazil. Between March 2008 and December 2009, 78 children and adolescents (6–16 years of age) with difficult-to-treat epilepsy, defined by at least one seizure in the previous 3 months despite adequate doses of at least two adequate antiepileptic drugs (AEDs), were screened with the Swanson, Nolan, and Pelham questionnaire version IV (SNAP-IV) [31] because of the presence of behavioral problems or difficulties at school. Thirty were excluded either because they did not have ADHD or because they did have significant ADHD symptoms but could not undergo IQ testing. Another 13 could not be included because of a progressive neurological disorder or a clinical disorder deemed incompatible with methylphenidate use. Two others were scheduled for epilepsy surgery in the following weeks, and the parents of three patients declined inclusion.

The 30 remaining patients engaged in the following evaluation procedures. First, a clinical interview to establish the diagnosis of ADHD and its subtype according to DSM-IV criteria was performed by two trained child neurologists. An independent trained rater then applied the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (K-SADS-PL) [32] to assess other potential psychiatric diagnoses, and a clinical committee (including a pediatrician, a psychologist, and two neurologists) reviewed the data to confirm the diagnosis of ADHD and to identify additional psychiatric disorders according to DSM-IV. The Brazilian version of the Wechsler Intelligence Scale for Children – WISC-III [33] – was used to determine the presence of mental retardation, based on a score of ≤69, according to International Statistical Classification of Diseases and Related Health Problems (ICD-10) [34].

To assess quality of life, we used a specific instrument based upon the 'Impact of Childhood Illness Scale' [35] that is validated for the Brazilian population (Quality of Life in Children with Epilepsy — QVCE) [36]. This is a 50-item questionnaire subdivided into four domains: physical, psychological, social, and cognitive–educational. Each item is scored 1–4, with higher scores indicating better quality of life in each domain. A general score based on all 50 items was also obtained. Results are reported as percentage of the total score in each and across all domains. Seizure severity was quantified at monthly visits (see below) with the Hague Seizure Severity Scale (HASS), an inventory of 13 ictal and postictal problems that is reliable in terms of test–retest stability and internal consistency [37]. Scores range from 13 (no seizures) to 52 (maximum seizure severity).

The Barkley Side Effects Rating Scale [38] was used to monitor adverse effects and adjust methylphenidate dosage. This scale probes 17 symptoms and scores each from 0 (absent) to 9 (severe). Three and 7 are the cutoff limits for mild and severe intensity, respectively, of a given symptom; scores 4–6 indicate medium severity.

The timetable for evaluative and interventional procedures is summarized in Fig. 1. Patients were seen at least four times in 6 months: at the outset of baseline (T − 3), 3 months later, when methylphenidate was started (T0), and then one (T + 1) and 3 (T + 3) months later. During the first 3 months (baseline period, T − 3 to T0), modifications in AED type and/or dosages were performed. At the outset of the baseline period, patients were evaluated with the SNAP-IV, QVCE, and HASS and also had their seizure frequency in the three previous months noted. Three months later (T0), methylphenidate was started and slowly titrated up at a rate of 2.5 mg/week in children weighing less and at 5 mg/week in children weighing more than 30 kg.

At this and each subsequent visit (T + 1 and T + 3), scores of the scales described above were obtained to monitor the evolution of

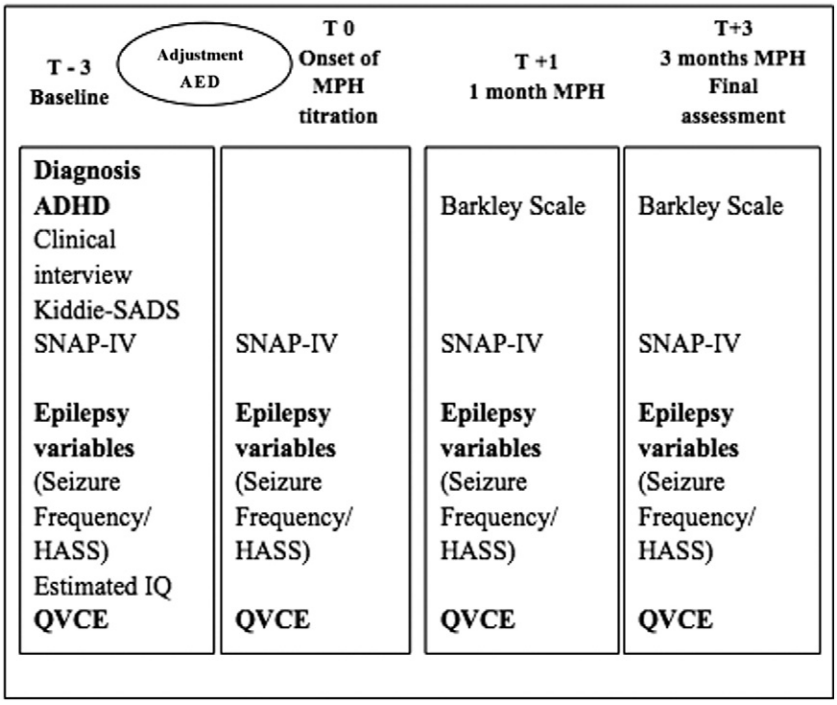

Fig. 1. Study outline. ADHD—attention-deficit/hyperactivity disorder, Barkley—adverse events MPH scale, HASS—Hague Seizure Severity Scale, IQ—intelligence quotient (WISC), Kiddie-SADS—Schedule for Affective Disorders and Schizophrenia for School-Age Children, MPH: methylphenidate, QVCE—Quality of Life in Children with Epilepsy, and SNAP-IV—ADHD symptom scale. Seizure frequency was the monthly average for the duration of the interval.

ADHD symptoms (SNAP-IV), quality of life (QVCE), seizure severity (HASS), and side effects (Barkley Scale).

Three of the 30 patients did not complete the trial: one had severe headache between T + 1 and T + 3, another one had seizure frequency that increased significantly between T0 and T + 1 (this patient had an average of 5 seizures/month during baseline and had 8 seizures already in the first week with methylphenidate), and the last one had an episode of aggressiveness following methylphenidate onset (between T0 and T + 1). These three patients were included in the intention-to-treat analysis as 'last observation carried forward' (LOCF).

Safety measures included providing the researchers' mobile phone numbers to parents, neurology residents, and emergency room staff. Parents were instructed to call or present to the emergency room should generalized seizures or any other serious side effects occur. In addition, they were informed about the objectives and risks of the study, particularly the risk of more frequent or severe seizures, and patient inclusion occurred only after their formal agreement. The study was approved by the Ethics Committee of our institution.

2.2. Statistical analyses

Quantitative data were referred to as means and standard deviation or median and interquartile amplitude, according to the symmetry of the distribution, and analyzed with the Shapiro–Wilk test. Associations between quantitative variables were tested with Pearson's or Spearman's linear correlation. Means were compared with Student's t-test or one-way ANOVA if data were derived from two or more groups, respectively. Comparison of scores obtained at each of the four visits was performed through repeated measures ANOVA with post hoc Bonferroni correction for data with symmetric distribution or with Friedman's test with post hoc Wilcoxon correction, adjusted by Finner, for asymmetrical data. A multiple linear regression backward model was used to control for confounding factors and identify variables independently associated with quality of life. Variables were entered in the model if they had $p < 0.20$ in the bivariate analysis. Analyses were performed with SPSS (Statistical Package for the Social Sciences) version 17.0 and PEPI (Programs for Epidemiologists) version 4.0. Significance level was established at 5%. A sample size of 20 patients assessed before and after the intervention was determined, aiming at an alpha of 0.05 and a power of 90% to detect a 1 standard deviation difference in the global score of the QVCE.

3. Results

Table 1 describes the sample. The mean age at seizure onset, mean age at inclusion in the study, and duration of epilepsy were, respectively, 29 months, 11.5 years, and 7.7 years. Two-thirds were male, with mean IQ of 75. Eight patients had a history of severe perinatal hypoxia with diffuse or localized MRI atrophic lesions. Another eight had malformations of cortical development or tuberous sclerosis, some of whom were being considered for surgical treatment; two had bilateral asymmetrical hippocampal malformations; and the other 12 did not have structural lesions identified on MRI.

3.1. Seizure frequency and severity

Intention-to-treat analysis with LOCF, including the three patients who did not complete the study, showed a significant reduction in seizure frequency and severity from baseline (T − 3) to 1 month after methylphenidate onset (T + 1) ($p < 0.001$), with stabilization between 1 and 3 months with the stimulant medication (Table 2). More specifically, significant reductions were observed not only between T − 3 and T0, i.e., after AED adjustments but before methylphenidate onset, but also between T0 and T + 1, suggesting an additional effect of methylphenidate on seizure control, which remained stable for the ensuing months (Table 2).

Table 1
Clinical and sociodemographic characteristics of the sample.

Variables	n = 30
Age (years) — mean ± SD	11.5 ± 3.3
Age at onset of seizures (months) — median (IR)	29 (4–61)
Epilepsy duration (years) — median (IR)	7.8 (5–10.9)
Gender — n (%)	
Male	20 (66.7)
Female	10 (33.3)
Epilepsy syndrome — n (%)	
Generalized	10 (33.3)
Partial	19 (63.3)
Unknown	1 (3.3)
Etiology — n (%)	
Cryptogenic	13 (43.3)
Symptomatic	16 (53.3)
Idiopathic	1 (3.3)
IQ (WISC-III) — mean ± SD [range]	75.3 ± 24.0 [51.3–99.3]

IR = interquartile range.

3.2. ADHD symptoms

Data in Table 2 show the evolution of ADHD symptoms during the study, in particular the lack of symptomatic effect of AED adjustments before methylphenidate use (T − 3 until T0).

3.3. Dosage of methylphenidate

Before adjustments dictated by side effects in five patients, the mean dose of methylphenidate reached 0.39 ± 0.18 mg/kg (range: 0.12 to 0.83), whereas at the end of the study, the mean dose was 0.40 ± 0.15 mg/kg (range: 0.13 to 0.80 mg/kg; $p = 0.56$).

3.4. Quality of life

Quality of Life in Children with Epilepsy scores did not change significantly during baseline following adjustments in AED treatment. However, 1 and 3 months after introduction of methylphenidate, a marked increase in quality-of-life scores compared to the 3 months of baseline was noted, encompassing all domains ($p < 0.001$). These scores did not significantly differ between 1 and 3 months after stimulant onset, except for the cognitive domain which improved further (Table 2).

Multivariate linear regression showed that alleviation of ADHD symptom burden, female sex, and tolerability to methylphenidate correlated with global scores in the quality-of-life scale (Table 3). The greater the reduction in SNAP-IV scores, the higher the QVCE scores. Furthermore, girls and patients who did not need to decrease methylphenidate doses because of side effects had, respectively, a probability of 8% and 11% increase in their quality-of-life scores. As the variables accepted by the model (Table 3) were more related to ADHD than to epilepsy (e.g., seizure frequency and severity), our findings suggest that the former bears a closer relationship to the quality-of-life scores in patients with this comorbidity. Fig. 2 details global and domain-specific quality-of-life scores before and after MPH.

4. Discussion

There is a consensus that neurologists need to pay more attention to the psychiatric comorbidities of epilepsy. Not only are these comorbidities frequent, but they also challenge superficial assumptions about suffering in patients with epilepsy, and a growing number of studies has been demonstrating that quality of life may relate more to behavior than to seizure variables. For instance, Choi-Kwon et al. showed that the presence of comorbid depression is a better predictor of quality of life than seizure control [39].

Table 2
Seizure, ADHD, and quality-of-life scores before and after methylphenidate (values presented as median (interquartile range)).

	−3 months (baseline, T − 3)	MPH onset (T0)	+1 month (T + 1)	+3 months (T + 3)	p-Value
SNAP-IV					
Hyperactivity	1.72 (1.22–2.18)[b]	1.55 (0.88–2.03)[b]	0.72 (0.30–1.17)[a]	0.77 (0.22–1.25)[a]	<0.001*
Inattention	2 (1.69–2.33)[b]	1.94 (1.69–2.33)[b]	1.32 (0.77–1.69)[a]	1.06 (0.77–1.58)[a]	<0.001*
ODD	1.25 (0.30–1.81)[b]	0.56 (0.09–1.62)[b]	0.37 (0.00–0.78)[a]	0.37 (0.00–0.78)[a]	<0.001*
QVCE#					
Global	61.5 ± 8.64[a]	64.4 ± 8.68[a]	72.6 ± 11.7[b]	75.7 ± 11.8[c]	<0.001**
Physical	59.8 ± 13.3[a]	62.6 ± 14.6[a]	71.9 ± 15.5[b]	74.3 ± 14.8[b]	<0.001**
Psychological	64.8 ± 9.89[a]	68.4 ± 9.00[a]	75.5 ± 11.5[b]	75.8 ± 13.2[b]	<0.001**
Social	66.7 ± 19.0[a]	69.1 ± 18.5[a]	77.7 ± 18.4[b]	79.2 ± 17.4[b]	<0.001**
Cognitive–educational	56.6 ± 14.9[a]	59.1 ± 14.9[a]	68.0 ± 15.3[b]	72.8 ± 13.9[c]	<0.001**
Seizures					
Frequency	6.5 (1–20)[c]	2 (0–9.0)[b]	0 (0–2.0)[a]	0 (0–4)[a]	<0.001***
Severity	29 (24–35)[c]	24 (13–31)[b]	13 (13–24)[a]	13 (13–25)[a]	<0.001***

QVCE = Quality of Life in Children with Epilepsy, and SNAP-IV = ADHD symptoms scale. Seizure severity was measured according to the HASS. Seizure frequency was the monthly average for the duration of the interval.
* Friedman test; a and b — same letters mean no difference by Wilcoxon correction adjusted by Finner at 5% ($p < 0.05$).
** Repeated measures ANOVA; a, b, and c — same letters mean no difference by Bonferroni correction at 5% ($p < 0.05$).
*** Friedman test; a, b, and c — same letters mean no difference by Wilcoxon correction adjusted by Finner at 5% ($p < 0.05$).
\# Described by mean ± standard deviation.

Attention-deficit/hyperactivity disorder is highly prevalent in children and adolescents with epilepsy in general, but particularly in those with difficult-to-treat epilepsies, and the negative impact of this comorbidity has been demonstrated [6,7,12,13]. However, the pharmacological management of ADHD in the context of difficult-to-treat epilepsies is plagued by the commonly held view that stimulants may worsen seizure control [23,30]. Therefore, data on the possible impact of treating ADHD symptoms with stimulants on the quality of life of these children are lacking.

Within the limitations of an open-label, uncontrolled trial, our results suggest that low to moderate doses of methylphenidate significantly reduce ADHD symptoms and improve quality of life in children and adolescents with difficult-to-treat epilepsies. Furthermore, as detailed elsewhere [25], treatment with methylphenidate was an adjuvant to AEDs in reducing seizure frequency and severity instead of an obstacle to seizure alleviation (Table 2).

As preliminary as these findings should be taken, they shed light on a number of issues that deserve more careful scrutiny in the future. First and foremost, the data suggest that adequately treating ADHD symptoms in patients with difficult-to-treat epilepsies leads to improvement in quality of life similar to that observed in ADHD children without epilepsy [39].

The practical relevance of this, if confirmed by future research, cannot be overemphasized because these children face several levels of limitation in their quest for social integration and learning, including the seizures, the cognitive handicap, and the ADHD symptoms. Not uncommonly, despite aggressive and adequate AED management, seizures cannot be completely controlled and cognitive limitations may also not be reversible. Our findings confirm and extend previous investigations showing that methylphenidate can be successfully used to treat children with severe epilepsy and comorbid ADHD with or without learning disability (IQ < 70) [40]. Therefore, reducing ADHD symptoms can be of great value and, not surprisingly, did appear to have a significant impact on quality of life.

Second, the data suggest that in patients with ADHD and difficult-to-treat epilepsies, AED adjustments alone do not significantly impact on quality of life despite reducing seizure frequency and severity. These preliminary findings not only agree with reports indicating that behavior is a better predictor of quality of life in epilepsy than seizures [16] but also suggest that seizure improvement without behavior improvement brings only limited benefit for patients and families. Should these findings be confirmed, they imply that not making the diagnosis and therefore not starting treatment of ADHD symptoms in patients with severe epilepsies does not meet their needs and is insufficient for improving their quality of life. Furthermore, they would urge neurologists to screen for ADHD and managers to provide comprehensive multidisciplinary care in tertiary outpatient clinics to identify and treat these patients.

Third, although three of the 30 patients had to discontinue methylphenidate and withdraw from the study because of significant headache, aggressiveness, and seizure worsening, respectively, the majority completed the trial. Thus, although these not unexpected adverse events do occur in this population, they do not rise to the level of considering methylphenidate as inadequate or unsuitable to treat ADHD in patients with epilepsy. In this respect and contrary to the preconceived view that methylphenidate worsens seizure control, the medication appeared to have a positive effect on seizure frequency and severity, which was additional to that of established AEDs. Along these lines, the improvement in seizure control was maintained during months 1 to 3 of methylphenidate use, reducing the possibility that this was a transient effect and supporting the finding that methylphenidate did not negatively interfere with seizure control. Additional studies with a placebo control group may clarify whether the prevalence and type of severe adverse events are significantly greater or more frequent in patients with epilepsy who use stimulant medication.

Quality of life improved through all domains of the QVCE after introduction of methylphenidate and remained stable during maintenance, between months 1 and 3, except for the cognitive domain, which improved further. This stabilization is expected in the short-term, and future studies should focus on the long-term effects of methylphenidate treatment in this population. In particular, such studies may clarify whether there is a ceiling effect to the positive impact of stimulant medications on the quality of life of patients with severe epilepsy,

Table 3
Multivariate linear regression with backward estimation to identify variables independently associated with quality of life (QVCE scores).

	Variables	Regression coefficient (b)	95% CI	Beta (β)	p-Value
Global QVCE	Female sex	8.04	−1.76 to −13.31	−0.455	0.004
	MPH adjustment	−10.78	−17.44 to −4.13	−0.482	0.003
	ΔInattention, T − 3 to T + 3	−5.32	−9.52 to −1.12	−0.380	0.015

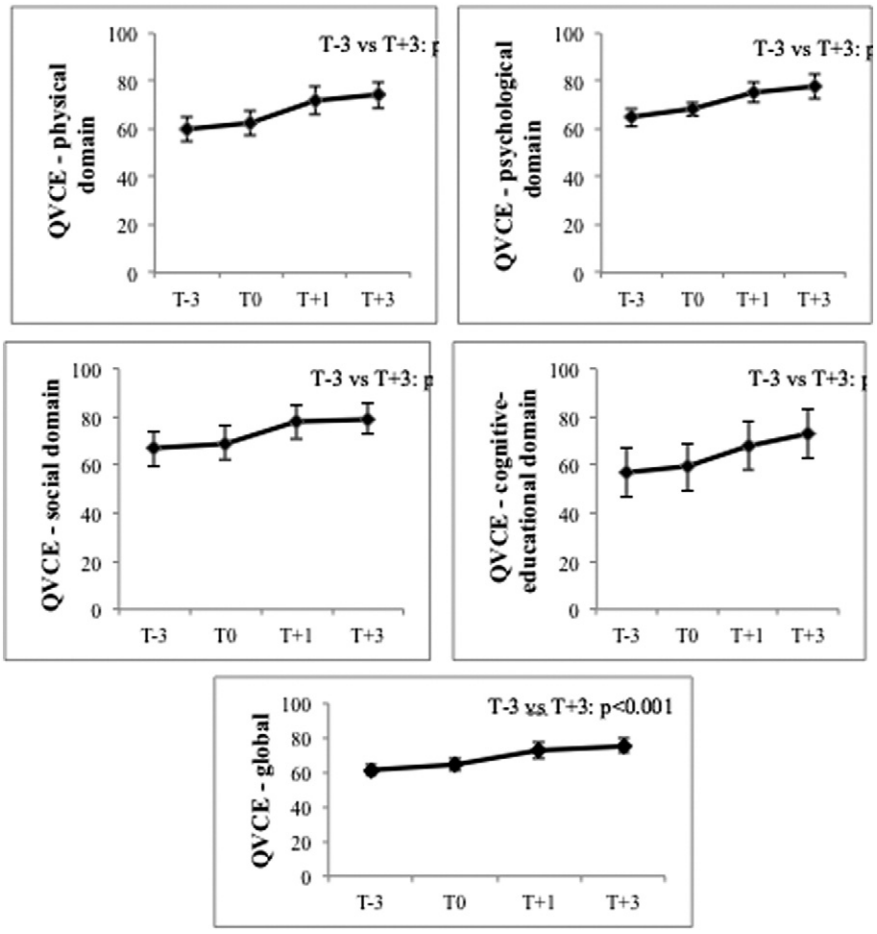

Fig. 2. Global and domain-specific quality of life in children with epilepsy (QVCE) at each evaluation. Circles indicate mean scores, and error bars represent lower and upper limits of the 95% confidence interval.

which is likely, given the broad range of limitations also imposed by the epilepsy itself and other cognitive handicaps.

Multivariate analysis raised further issues to be explored in the future. Female sex, level of improvement in ADHD symptoms, and tolerability to methylphenidate were retained in the regression model as variables significantly correlated with improvement in quality-of-life scores. Patients who needed to reduce methylphenidate dose because of side effects had around 11% lower scores in the general quality of life and 16% lower scores in the psychological domain compared to those who tolerated the therapeutic doses established with the titration schedule. This may suggest that some patients need higher doses of methylphenidate to control their symptoms and to positively impact on quality-of-life measures.

However, this should not detract from the main finding that even low to moderate doses of methylphenidate, around 0.40 to 0.50 mg/kg/day, proved sufficient to provide significant ADHD symptom alleviation and improvement in quality of life and did not interfere negatively with seizure control in this population.

Finally, some variables correlated with scores in specific domains of the QVCE. The presence of significant hyperactive symptoms at baseline and later age at epilepsy onset correlated with higher scores in the cognitive–educational domain, and a history of generalized tonic–clonic seizures reduced scores in the physical domain. Taken as a whole, these findings suggest that the earlier and the more severe the impact of the epilepsy, the lower the chances of improvement in quality of life, even if treating for ADHD symptoms. These results, however, must be replicated in larger samples with a more sophisticated study design. Also, they suggest that hyperactive symptoms do respond significantly to methylphenidate in these doses, and thus, their presence leads to higher chances of improvement in quality of life.

A major limitation of open-label, noncontrolled trials is that outcome is apparently related to the intervention because other alternatives are not tested. Thus, because we did not have a control group, we cannot rule out the possibility that adjustments of AEDs alone would have resulted, gradually, in the same level of improvement in quality of life as observed with methylphenidate. Nonetheless, the fact that such improvement was not observed in the first 3 months of the study, before methylphenidate was started but after AEDs were adjusted, renders this possibility less likely, although we cannot exclude it convincingly. Furthermore, open-label trials may have verification biases, particularly in studies in which outcome is a subjective variable depending exclusively upon the person being interviewed. Participants may systematically 'bias' their responses to the whole context of the study, including the expectations involved. Finally, there is another possibility of verification bias because the main questionnaire, the QVCE, is not self-applicable, lending it vulnerable to interviewer bias. The latter is even more relevant in open trial designs when participants and interviewers are aware of the intervention. Nevertheless, this is a bias difficult to avoid in studies using semistructured questionnaires.

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