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Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery



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Summary This retrospective study evaluates the impact of postoperative antiepileptic drug (AED) withdrawal on psychomotor speed in seizure-free children, operated for medically refractory epilepsy. Post-surgical medication policy and neuropsychological assessments (performed shortly before and 6, 12 and 24 months after surgery), were evaluated in 57 children (32 female, median age at surgery 13 years). Patients were divided into a withdrawal ($n=29$) and a no-withdrawal group ($n=28$). Scores of four psychomotor tests performed at 12 and 24 months after surgery were compared with those of postoperative baseline measurements, performed 6 months after surgery. At 24 months, the withdrawal group had improved significantly more than the no-withdrawal group on three of four tests; reaction time to light ($p=0.031$), reaction time to sound ($p=0.045$) and tapping ($p=0.003$). At 12 months, a non-significant tendency in the same direction was found for both reaction time tests. Drug withdrawal after surgery improves psychomotor speed and may unleash the potential for cognitive improvement.

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Introduction

The ultimate goal of epilepsy surgery in children is to reach “cure”, defined as both seizure- and antiepileptic drug (AED) freedom (Schmidt et al., 2004). In contrast to previous suggestions that early withdrawal would be unsafe, we recently demonstrated in a large retrospective European cohort study that timing of postoperative AED

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discontinuation in children did not relate to long-term seizure outcomes (Boshuizen et al., 2012). Antiepileptic drug withdrawal might not only be safe but also beneficial with regard to cognitive functioning, since AEDs are known to have cognitive side effects (Loring and Meador, 2004), with attention, vigilance and psychomotor speed being most affected (Meador, 2002). From medically treated cohorts of seizure free patients, we know that AED discontinuation leads to improved complex cognitive processing under time pressure in adults (Lossius et al., 2008) and increased psychomotor speed and higher alertness in children (Aldenkamp et al., 1993, 1998). Less is known about cognitive benefits of AED withdrawal after epilepsy surgery, but AED cessation was recently shown to be the strongest predictor of postoperative increase in IQ in children who underwent temporal lobe surgery (Skirrow et al., 2011). Here, we aimed to evaluate the effect of postoperative AED withdrawal on psychomotor speed in seizure free children after epilepsy surgery.

Material and methods

We retrospectively evaluated postoperative cognitive functioning and medication policy in children who underwent epilepsy surgery in our center between 1998 and 2010. Cognitive functioning was monitored by neuropsychological assessments at fixed time points, shortly before and 6, 12 and/or 24 months after surgery (pre-NPA, NPA6, NPA12 and NPA24). Postsurgical use of AEDs was obtained from the patients' medical or neuropsychological records. Patients were included if they (1) underwent at least two postoperative NPAs, including NPA6, (2) were 6 years or older at the time of pre-NPA; the lowest age level at which the assessed psychomotor tests were performed, (3) had a total IQ of at least 55 at NPA6, as most children with an IQ < 55 are not able to perform the psychomotor tests used, due to their low level of cognitive functioning and (4) reached complete seizure-freedom after surgery.

For each patient, available performances with their dominant hand on four psychomotor speed tasks were collected: (1) simple reaction time to light (milliseconds [ms]), (2) simple reaction time to sound (milliseconds [ms]), (3) Purdue pegboard test (seconds [s]), and (4) tapping (number of taps [n]). These tasks were part of the reaction time test (1 and 2) and motor performance series (3 and 4) of the Vienna Test System (Schuhfried, Vienna).

To exclude possible bias through differential effects of the surgical procedure itself on the course of cognitive functioning between groups, we used the first postoperative time point (NPA6) as baseline (rather than preoperative assessment). Using this baseline, changes in postoperative psychomotor speed were assessed by calculating differences in raw scores between the later assessments (NPA12 and NPA24) and baseline. Subsequently, these raw delta-scores were expressed as percentages (improvement or deterioration) of the baseline score.

Patients were categorized in two groups. "Withdrawal" was defined as complete cessation of at least one AED at the latest time of assessment (NPA12 or NPA24) compared to the number of AEDs used at NPA6. "No-withdrawal" was

defined as continuation of all AEDs that were used at baseline assessment.

Statistical analyses were performed using SPSS, version 20. Mann–Whitney *U* and chi-square tests were used for comparing baseline characteristics of both groups. Independent-samples *t*-tests were conducted to compare the mean percentage deltascores of the "withdrawal" group and the "no-withdrawal" group. The significance level was set at $p < 0.05$ (two-tailed).

Results

Of the 57 included patients, 29 (51%) withdrew at least one AED and 28 (49%) did not discontinue medication after NPA6. Thirteen patients (23%) were completely AED-free at NPA24. Patient characteristics of both groups are shown in Table 1. Extra-temporal surgery was performed more often in the "withdrawal" group than in the "no-withdrawal" group. A tumor was the most common underlying cause of epilepsy in both groups. More children in the no-withdrawal group used only one AED at baseline. Gender, age at onset and surgery, side of surgery and TIQ were not different between the two groups.

As we used mean delta-scores to compare the individual test results of latest NPA with baseline-assessment in both groups, instead of direct cross sectional comparison of the groups, we did not control for baseline differences.

Changes in scores on the four psychomotor tests are shown in percentage delta-scores in Table 2. Except for Purdue pegboard, there were significant differences in delta-scores between the withdrawal- and the no-withdrawal group, 24 months after surgery, in favor of the withdrawal group. At NPA24, the mean delta-score for the reaction time to light test, was -15.7% in the withdrawal group, compared to -1.8% in the no-withdrawal group ($p = 0.031$); the mean delta-score for the reaction time to sound test in the withdrawal group was -12.4% versus -5.6% in the no-withdrawal group ($p = 0.045$) and the mean delta-scores for the tapping test were 12.2% and 3.4% respectively ($p = 0.003$). At NPA12 a non-significant tendency in the same direction was seen for both the reaction time to sound and light test.

Discussion

The main finding of this retrospective study is that postoperative AED withdrawal in children significantly improves performances on psychomotor speed tests. Two years after surgery, the children who discontinued at least one AED improved significantly more on several psychomotor speed tests compared to 6 months postoperatively, than children who remained on medication.

Two previous AED discontinuation studies in non-surgical pediatric cohorts have reported varying effects on cognition. Chen et al. (2001) found no correlation between AED withdrawal and IQ in a nonrandomized and unblinded discontinuation study in 70 seizure-free children on monotherapy. Aldenkamp et al. (1993, 1998) reported significant improvement of psychomotor speed and observed subjective improvement in alertness in 83 seizure-free children on monotherapy who withdrew medication.

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