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Temporopolar blurring in temporal lobe epilepsy with hippocampal sclerosis and long-term prognosis after epilepsy surgery

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Summary
Purpose: We conducted a retrospective study in order to investigate the clinical significance of temporopolar grey/white matter abnormalities (GWMA) in patients with temporal lobe epilepsy (TLE) and unilateral hippocampal sclerosis (HS) with a long post-surgical follow-up.
Methods: The study comprised 122 consecutive patients with medically refractory TLE and unilateral HS who underwent epilepsy surgery and had a minimum postoperative follow-up of 5 years. Patients were divided into two groups, based on findings of pre-surgical MRI: group 1 with GWMA and 2 with normal signal and grey/white matter definition in temporal pole. Demographic and clinical data were reviewed and compared between groups.
Results: GWMA were found in 52.5% of patients, always ipsilateral to HS. Compared with group 2, group 1 patients had earlier epilepsy onset (mean, 9.3 vs 14.4 years, $P = 0.001$), a higher occurrence of first seizure $\leq$2 years of age (25.8% vs 10.5%, $P = 0.036$; OR = 2.96 [95% CI = 1.07—8.19]), and greater prevalence of left HS (76.6% vs 43.1%, $P < 0.001$; OR = 4.31 [95% CI = 1.98—9.38]). No differences were found in gender, presence or type of initial precipitating injury, history of secondary generalized seizures, duration of epilepsy, seizure frequency before surgery, neuropsychological evaluation and presence or lateralization of pre-surgical interictal epileptiform discharges. Postoperative follow-up varied from 5 to 11.5 years (mean 7.4) and was similar in

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both groups ($P = 0.155$). The proportion of patients classified as seizure-free (Engel class I) at last follow-up in groups 1 and 2 were 73.4% and 69%, respectively ($P = 0.689$). Similarly, the percentages of seizure-free patients with no antiepileptic drugs at last evaluation were not different between groups ($P = 0.817$). In logistic regression analysis, left HS ($P = 0.001$; OR = 4.166 [95% CI = 1.86—9.34]) and age at epilepsy onset $\leq$2 years ($P = 0.047$; OR = 3.885 [95% CI = 1.86—17.50]) were independently associated with risk of having GWMA.
Conclusion: GWMA are frequent findings in patients with TLE and HS, and may help lateralize the epileptogenic zone. Our data support the hypothesis that GWMA are caused by seizure-related insults during the critical period of cerebral myelination. GWMA did not influence the postoperative seizure outcome of patients with TLE and HS, even after an extended duration of post-surgical follow-up.

Introduction

Temporal lobe epilepsy (TLE) is the most prevalent refractory focal epilepsy syndrome in adults (Engel, 1996; Semah et al., 1998) and hippocampal sclerosis (HS) its main pathological substrate (Junna et al., 2013; Wiebe et al., 2001; Williamson et al., 1993).

Temporopolar grey/white matter abnormalities (GWMA) are abnormal findings observed on MRI in patients with TLE and are described as increased signal intensity in the white matter together with loss of grey/white matter demarcation on T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences. These MRI abnormalities (also called 'grey/white matter blurring') may be associated with temporal pole atrophy (Coste et al., 2002; Mitchell et al., 1999) and are mostly found in patients with HS, with a frequency ranging from 32% to 75% (Carrete et al., 2007; Choi et al., 1999; Mitchell et al., 1999).

GWMA have been associated with different histopathological findings, such as focal cortical dysplasia (Kuba et al., 2012), increased number of heterotopic neurons in the white matter (Choi et al., 1999) and significantly reduced white matter staining, suggesting myelin loss (Meiners et al., 1999). A recent study, using high-field (7T) MRI combined with light and electron microscopy of surgical specimens resected from nine drug-refractory patients with TLE and HS, demonstrated a significantly reduced number of fibres in the subcortical white matter and a smaller percentage of the area occupied by myelinated axons in patients with GWMA, with the residual myelinated fibres not showing any substantial alteration in the myelin sheath (Garbelli et al., 2012).

The clinical significance of temporopolar signal abnormalities has not yet been established. GWMA have been associated with earlier epilepsy onset (Carrete et al., 2007; Choi et al., 1999; Garbelli et al., 2012; Mitchell et al., 2003; Schijns et al., 2011), with conflicting data concerning epilepsy duration (Carrete et al., 2007; Choi et al., 1999; Garbelli et al., 2012; Mitchell et al., 1999, 2003; Schijns et al., 2011). Post-surgically, Choi et al. (1999) found a significant higher proportion of seizure-free patients in the group with GWMA, whereas other studies (Carrete et al., 2007; Garbelli et al., 2012; Kuba et al., 2012; Mitchell et al., 1999; Schijns et al., 2011) showed no differences in postoperative seizure outcomes. Garbelli et al. (2012) could not demonstrate GWMA influence in the outcome, suggesting that it would be interesting to evaluate in a large cohort of patients with a longer follow-up after surgery if white matter blurring would represent a sign of worse surgical prognosis, supporting the hypothesis of the organization of a new epileptogenic zone outside the excised tissue.

The aim of this study was to investigate the clinical correlations of anterior temporal signal changes in patients with TLE and HS who had surgery due to drug-refractory epilepsy. Particularly, we examined, in a long post-surgical follow-up, the impact of GWMA on postoperative seizure outcome.

Patients and methods

Patients

This retrospective study included consecutive patients with medically refractory TLE (Commission, 1989) and MRI findings of unequivocal unilateral HS, represented by visual hippocampal atrophy and FLAIR/T2 hypersignal on coronal images, who underwent surgery between 2002 and 2008 at Hospital São Paulo, Universidade Federal de São Paulo, São Paulo, Brazil. Seizures were qualified as medically refractory when they persisted despite adequate use of at least two tolerated first-line antiepileptic drugs (AEDs), in mono or polytherapy (Kwan et al., 2010). A minimum postoperative follow-up of 5 years was required. Patients with imaging evidence of bilateral HS or other lesions (tumours, vascular malformations, scars, etc.), except cysticercosis calcifications, were excluded. Patients were divided into two groups, based on the findings of pre-surgical MRI evaluation: those with GWMA (group 1) and patients with normal signal and grey/white matter definition in temporal pole (group 2). Demographic and clinical data, including postoperative seizure status, were obtained by medical chart review. Informed consent of the patients was obtained before pre-surgical and surgical procedures were performed. The study was approved by the local ethics committee.

Pre-surgical evaluation

All patients underwent a complete pre-surgical evaluation at the epilepsy monitoring unit at Hospital São Paulo, which included: detailed history, with characterization of initial