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# Structural brain abnormalities in epilepsy with myoclonic atonic seizures

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ABSTRACT

*Objective:* Epilepsy with myoclonic atonic seizure (EMAS) occurs in young children with previously normal to subnormal development. The outcome ranges from seizure freedom with preserved cognitive abilities to refractory epilepsy with intellectual disability (ID). Routine brain imaging typically shows no abnormalities. We aimed to compare the brain morphometry of EMAS patients with healthy subjects several years after epilepsy onset, and to correlate it to epilepsy severity and cognitive findings.
*Methods:* Fourteen EMAS patients (4 females, 5–14 years) and 14 matched healthy controls were included. Patients were classified into three outcome groups (good, intermediate, poor) according to seizure control and cognitive and behavioral functioning. Individual anatomical data (T1-weighted sequence) were processed using the FreeSurfer pipeline. Cortical volume (CV), cortical thickness (CT), local gyrification index (LGI), and subcortical volumes were used for group-comparison and linear regression analyses.
*Results:* Morphometric comparison between EMAS patients and healthy controls revealed that patients have 1) reduced CV in frontal, temporal and parietal lobes ($p = <.001$; 0.009 and 0.024 respectively); 2) reduced CT and LGI in frontal lobes ($p = 0.036$ and 0.032 respectively); and 3) a neat cerebellar volume reduction ($p = 0.011$). Neither the number of anti-seizure medication nor the duration of epilepsy was related to cerebellar volume (both $p > 0.62$). Poor outcome group was associated with lower LGI. Patients in good and intermediate outcome groups had a comparable LGI to their matched healthy controls ($p > 0.27$ for all lobes).
*Conclusions:* Structural brain differences were detectable in our sample of children with EMAS, mainly located in the frontal lobes and cerebellum. These findings are similar to those found in patients with genetic/idiopathic generalized epilepsies. Outcome groups correlated best with LGI. Whether these anatomical changes reflect genetically determined abnormal neuronal networks or a consequence of sustained epilepsy remains to be solved with prospective longitudinal studies.

## 1. Introduction

Epilepsy with myoclonic atonic seizures (EMAS) (OMIM *616421), formerly known as myoclonic-astatic epilepsy or Doose syndrome, is a generalized epilepsy syndrome of childhood. It is characterized by the following clinical and EEG features : onset of myoclonic atonic seizures typically between two to four years (range six months to six years) in children with normal or nearly normal development prior to seizure onset and who may have a history of febrile or afebrile seizures, frequent status epilepticus, a 2:1 male:female ratio, initial normal electroencephalogram (EEG) evolving to generalized polyspikes and waves complexes (Anon, 2021). No structural abnormalities are found on brain MRI and etiology is still elusive, but a genetic origin with complex inheritance is likely (Tang and Pal, 2012). To date, explanatory genes have been identified in a minority of EMAS patients (Carvill et al., 2015; Mullen et al., 2011; Routier et al., 2019).

The course of the disease is variable. Developmental plateauing or regression affecting attention, speech, language, motor coordination,

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and behavior is frequent during the active phase of the epilepsy. These cognitive and behavioral impairments usually improve once seizures are controlled, suggesting a negative impact of the epileptic activity on brain function (Deonna, 2005), i.e, an epileptic encephalopathy. General outcomes range from seizure freedom and normal intelligence to refractory epilepsy with mild to moderate intellectual disability (Caraballo et al., 2013; Oguni et al., 2002). Up to sixty percent of the children with EMAS have an intelligence within the normal range, but neuropsychological difficulties including attention deficit, impulsivity, and repetitive behaviors, even on the long-term may be observed (Filippini et al., 2006). Patients with refractory epilepsy after three years of follow-up often display intellectual disability (Caraballo et al., 2013; Oguni et al., 2002; Kaminska et al., 1999; Lebon et al., 2015). The presence of afebrile generalized tonic-clonic seizures during the first 2 years of life, non-convulsive status epilepticus, tonic vibratory seizures, focal discharges or failure to develop a normal background alpha rhythm on the EEG were reported as risk factors for an unfavourable outcome (Caraballo et al., 2013; Kaminska et al., 1999; Inoue et al., 2014; Kelley and Kossoff, 2010).

Pathophysiological mechanisms underlying EMAS remain unknown. A genetically determined cortico-reticular network hyperexcitability generating spike–and-wave complexes has been postulated (Doose, 1992; Doose et al., 1967). A bilateral frontal generator located in the premotor cortex and involvement of the reticulospinal tracts in the brainstem was demonstrated by magneto-encephalography analyses during seizures (Kubota et al., 2004). Furthermore, the presence of cortical micro-dysgenesis has been hypothesized, based on focal EEG discharges in certain patients with poorer outcomes (Inoue et al., 2014). An EEG-functional MRI (fMRI) study showed changes in the thalamo-cortical network, premotor cortex, putamen and cerebellum (Moeller et al., 2014). However, so far, no study has used quantitative brain MRI analysis for investigation of structural abnormalities in EMAS patients. This approach aims to measure morphometric parameters such as cortical thickness (CT), cortical volume (CV) and folding via local gyrification index (LGI) as well as volume of sub-cortical structures (Fjell et al., 2015; Tamnes et al., 2017).

Regarding seizure types, EMAS resembles idiopathic generalized epilepsy syndromes (IGE) (Fisher et al., 2017; Scheffer et al., 2017) that include childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with tonic-clonic seizures, but age at onset is younger and seizures frequency is higher in EMAS. In IGE, visual inspection of brain MRI is also normal, but morphometric analysis approach showed whole-brain volume reduction, variable patterns of regional cortical and thalamus volume alterations (Perani et al., 2018; Whelan et al., 2018), cortical thickness changes and subtle cortical folding abnormalities predominantly in frontal and temporal areas (Perani et al., 2018; Whelan et al., 2018; Nuyts et al., 2017). Age of onset, duration of epilepsy and anti-epileptic medications may contribute to variation in findings in the different IGE subtypes (Masur et al., 2013; Ratcliffe et al., 2020).

This study aims to compare the brain's morphometry of children with EMAS to paired-match healthy controls several years after epilepsy onset, and correlate it to epilepsy and cognitive findings. As EMAS shares seizure types and EEG patterns with other IGE, we hypothesized that the underlying affected brain regions are similar.

## 2. Material and methods

### 2.1. Participants

Patients with EMAS were recruited from the pediatric neurology units of the Lausanne University Hospital (CHUV) and the Geneva Children's Hospital (HUG). Patients were aged between 5 and 14 years and diagnosed with EMAS by experienced pediatric neurologists. The diagnosis was based on the following criteria: myoclonic atonic seizures +/- other generalized seizures; diffuse (poly-)spike-wave complexes on EEG; seizure-onset between 6 months and 6 years; and a history of normal or almost normal development prior to seizure onset (speech and language delay and/or mild motor delay were accepted). Glucose transporter type 1 deficiency was excluded in all patients by *SLC2A1* sequencing and/or normal glycorrhachia on fasting lumbar puncture. Age of epilepsy onset, duration of epilepsy, anti-seizure medications (ASM), and neuropsychological testing results as well as language, cognitive and/or behavioral stagnation or regression were collected. The presence of stagnation or regression was based on parental reports and clinical assessments performed by experienced pediatric neurologists. Exclusion criteria were structural brain abnormalities on MRI or family refusal to participate in the study.

For group-comparison, each patient was matched based on his age and gender with data from a healthy control. These 14 controls were participants from a brain fMRI study and had no history of developmental delay or neurological disease such as epilepsy. (Denervaud et al., 2020)

The study protocols were approved by the ethical committee of both hospitals. Written informed consent from parents and oral consent from participants were obtained.

### 2.2. Clinical evaluation

All patients underwent routine clinical follow-up in their neuropediatric outpatient clinic and had at least one neuropsychological assessment including intellectual quotient (IQ) (Wechsler Preschool and Primary Scale of Intelligence –III and -IV, Wechsler Intelligence Scale -IV and –V) (Grizzle, 2011), language (Vocabulary-word definition and Comprehension tests from the Wechsler scales), executive functions (Day/Night Stroop task (Montgomery and Koeltzow, 2010), Color Trail and Trail Making tests (Spreen, 1998) and Mazes from the Wechsler scales) testing according to age. Patients were classified into three outcome groups based on epilepsy severity according to seizures control and presence of cognitive disorders. *Good*: no seizures, average intellectual quotient (IQ) (85–115) +/- minor executive and /or learning difficulties; *Intermediate*: no seizures, low average to borderline IQ (70–100), marked executive and learning difficulties; *Poor*: active epilepsy, intellectual disability (IQ $< 70$). The number of anti-seizure medication(s) (ASM) at the time of the study inclusion was computed (see Table 1).

### 2.3. MRI acquisition

Structural imaging was collected at the Biomedical Imaging Center (CIBM) of the Lausanne University Hospital (CHUV), on a Siemens 3 T Prisma-Fit MR scanner, with a 64-channel head-coil. For each participant, a 3-dimensional high-resolution isotropic T1-weighted sequence (MPRAGE) was acquired (TR = 2000 ms, TE = 2.47 ms, 208 slices; voxel size = $1 \times 1 \times 1$, flip angle = 8 °) as anatomical individual reference.

#### 2.3.1. Image processing

Individual T1-weighted sequence were processed using the FreeSurfer 5.1.0 software (surfer.nmr.mgh.harvard.edu), a commonly-used open-source software package. The pipeline includes a first step of brain extraction, automated Talairach transformation, brain tissue segmentation into white and grey matter and their boundaries, automated topological correction and deformation, and parcellation of cerebral cortex into anatomical structures automatically labelled into 34 regions per hemisphere (Fischl et al., 2004; Desikan et al., 2006). The second step computed voxels within each regions to derive morphometric measures (Fischl, 2012). For the current study, we focused on the cortical volume (CV; surface-based volume difference between the pial and the white matter surfaces), cortical thickness (CT; computed as the distance between the white matter and the pial surface) and local gyrification index (LGI: a metric that quantifies the amount of cortex buried

**Table 1**
Patients' demographical and clinical characteristics. *ASM:* anti-seizure medication. *IQ:* intellectual quotient.

| ID | Age (years) | Gender | Epilepsy Onset (months) | Epilepsy Duration (years) | ASM | Cognitive Stagnation/ Regression | IQ | Outcome group |
|---|---|---|---|---|---|---|---|---|
| 001 | 14 | M | 35 | 11 | 2 | yes | 45 | 3 |
| 002 | 11 | M | 25 | 2.6 | 0 | no | 90 | 2 |
| 003 | 10 | F | 47 | 0.6 | 1 | no | 88 | 2 |
| 004 | 10 | M | 30 | 1.5 | 1 | no | 102 | 1 |
| 005 | 12 | M | 28 | 5.2 | 2 | no | 94 | 1 |
| 006 | 8 | M | 38 | 4.9 | 4 | yes | 40 | 3 |
| 007 | 13 | M | 37 | 2.4 | 0 | no | 110 | 1 |
| 008 | 15 | F | 62 | 9.8 | 2 | yes | 56 | 3 |
| 009 | 10 | F | 27 | 7.8 | 1 | yes | 60 | 3 |
| 010 | 7 | M | 36 | 0.8 | 1 | no | 90 | 1 |
| 011 | 5 | M | 43 | 1 | 2 | no | 85 | 1 |
| 012 | 12 | M | 60 | 6 | 1 | no | 93 | 1 |
| 013 | 8.5 | M | 22 | 6.3 | 3 | no | 53 | 3 |
| 014 | 11 | F | 42 | Unknown | 1 | no | 82 | 2 |

within the sulcal folds as compared with the amount of cortex on the outer visible cortex. A cortex with extensive folding has a large gyrification index, whereas a cortex with limited folding has a small gyrification index) (Schaer et al., 2008) measures for whole-brain and lobes. The lobes were defined as in a previous study (Klein and Tourville, 2012), cingulate gyrus and insula were also included in our analyses (Ronan et al., 2012). We measured subcortical volumes from the putamen, globus pallidus, caudate, thalamus and cerebellum as well as global white matter volume with the automated pipeline for volumetric measures from Freesurfer.

### 2.4. Statistical analyses

Demographical, clinical and neuroimaging data were analyzed using the statistical software Jamovi (Jamovi Project, 2018).

#### 2.4.1. Demographic variables

We ran an independent samples *t*-test to compare age between patients and controls, as well as a chi-square to compare the two groups according to gender.

#### 2.4.2. Morphometric variables

All neuroanatomical measures were examined for normality using Shapiro-Wilk test. Independent t-tests were conducted to statistically evaluate group differences (patients vs controls) in CV, CT and LGI measures at the whole-brain level. Additionally, we controlled for individual differences in intracranial volume (Malone et al., 2015) by running ANCOVA on each measure with the estimated Total Intracranial Volume (Breen et al., 2018) as a covariate. eTIV was computed based the relationship between the intracranial volume and the Talairach linear transform (Buckner et al., 2004). We further refined our investigations in group differences using independent t-tests at the cortical lobes level, with a false discovery rate (FDR) *p*-value correction for multiple comparison at $q = 0.05$. Subcortical morphometric measures were also investigated through independent t-tests.

#### 2.4.3. Relation between morphometric variables and clinical measures

To determine if cortical and subcortical changes were related to clinical variables, we performed simple linear regression analyses in the patient group between each cortical and subcortical morphometric measures and epilepsy onset, epilepsy duration, existence of cognitive regression/stagnation, number of anti-epileptic drugs, as well as epilepsy outcomes, while controlling for age and gender. Each cerebral lobe was considered as independent and did not correct for multiple comparisons; effect of each variable within linear regression were controlled through the statistical model. Results with a $p < 0.05$ were considered significant.

## 3. Results

### 3.1. Demographic variables

Fourteen EMAS patients were included. Median age at inclusion was 10.5 years (range 5–15 years); four patients were girls. Median age of seizure-onset was 36.5 months (range 22–62 months); median duration of epilepsy at inclusion was 4.86 years (range 0.6–11 years); median IQ was 86.5 (range 40–110). Table 1 summarizes demographical and main clinical patient data and table S3 results from clinical and neuropsychological findings. Patients were distributed into different 3 outcome groups, as follows: *Good outcome*: six patients, median IQ 93.5 (range 85–110); *Intermediate outcome*: three patients, median IQ 88 (range 82–90); *Poor outcome*: five patients, median IQ 53 (range 40–60).

Healthy controls (n = 14) had a median age of 10.0 years (± 2.13; range 5–13); four were females. Patients and controls did not differ in age ($t(26) = 0.498$, $p = 0.623$) and gender ($\chi^2 = 0.00$, $p = 1.00$).

### 3.2. Morphometric variables

#### 3.2.1. Whole brain analyses

When compared with matched controls, EMAS patients had significantly reduced whole-brain CV ($t(26)$=-2.32, $p = 0.029$, Cohen's d= 0.88) and CT ($t(26)$=-2.12, $p = 0.044$, Cohen's d= 0.80), as well as decreased LGI ($t(26)$=-2.19, $p = 0.038$, Cohen's d= 0.83). These results were robust when further controlling for individual intracranial volume (all $p < 0.046$). Fig. 1 reports results for whole-brain cortical group comparison analyses.

#### 3.2.2. Lobes and cingulate gyrus analyses

After correcting for multiple comparisons, EMAS patients versus controls had significantly reduced CV in the frontal ($t(26)$=-4.06, $p < 0.001$, Cohen's d = 1.53), temporal ($t(26) = 3.28$, $p = 0.009$, Cohen's d= 1.24), and parietal lobes ($t(26)$=-2.71, $p = 0.024$, Cohen's d= 1.02), as well as in the cingulate gyrus ($t(26)$=-2.27, $p$=0.046, Cohen's d = 0.86). CV did not differ between the two groups in the insula and occipital lobes ($p > 0.20$).

CT and LGI differed between EMAS and controls in the frontal lobe only, where a significant decrease was observed in patients ($t(26)$=-3.00, $p = 0.006$, Cohen's d = 1.13; and $t(26)$=-2.27, $p = 0.032$, Cohen's d = 0.86, respectively). All other regions were not significantly different between the two groups ($p > 0.13$). Table S1 reports detailed statistical comparisons.

#### 3.2.3. Subcortical structures

Subcortical analyses showed a significant CV reduction ($t(26)$=-2.74, $p$=0.011, Cohen's d = 1.03) in the cerebellum in patients versus

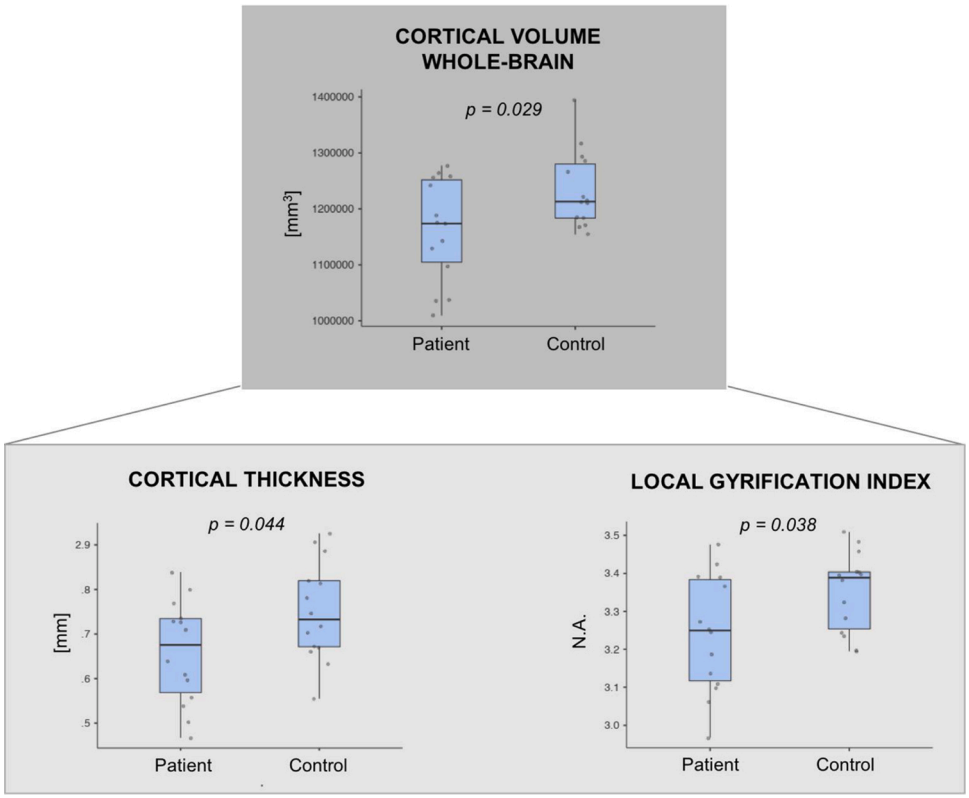


**Fig. 1.** Whole-brain group-comparison. Cortical volume (CV), thickness (CT) and local gyrification index (LGI) measures in patients compared to matched healthy controls.

controls. No other subcortical structures were significantly different between groups ($p > 0.25$; see Table S2). There was no differences in the global white matter volume between patients and control (t(26)=0.286, $p = 0.777$).

### 3.3. Relation between morphometric variables and clinical measures

Quantitative relation between morphometric measures and clinical variables were computed through linear regression analyses, controlling for age and gender.

Age at *epilepsy onset* correlated with frontal CV ($F(1,5) = 15.04$, $p = 0.012$), temporal CV ($F(1,5) = 10.05$, $p = 0.025$), and cingulate CV ($F(1,5) = 7.10$, $p = 0.045$), so that later onset was associated with reduced CV. *Epilepsy onset* correlated with frontal LGI ($F(1,5) = 8.64$, $p = 0.032$), temporal LGI ($F(1,5) = 13.79$, $p = 0.014$), cingulate LGI ($F(1,5) = 14.91$, $p = 0.012$), and insula LGI at trend-level ($F(1,5) = 6.34$, $p = 0.053$), so that later onset was associated with higher LGI.

Outcome groups correlated with frontal LGI ($F(1,5) = 8.55$, $p = 0.033$) and temporal LGI ($F(1,5) = 11.77$, $p = 0.019$): lower LGI were related to *poor* outcome group (Fig. 2). In fact, patients with a *good* and *intermediate* outcome had a comparable LGI to their matched healthy controls ($p > 0.27$ for all lobes). No correlations between outcome groups and cerebellar volume was observed ($p$=0.79).

*Number of ASM* correlated with cingulate CT ($F(1,5) = 7.40$, $p = 0.042$), and temporal CT at trend-level ($F(1,5) = 6.05$, $p = 0.057$), so that an increased number of ASM was associated with relatively thicker cortex. The *number of ASM* did not correlate with cerebellar volume ($p = 0.71$). *Epilepsy duration* and *cognitive stagnation/regression* did not correlate with morphometric measures (all $p > 0.05$).

## 4. Discussion

Significant morphometric brain alterations were found in our cohort of children with EMAS, as compared to healthy controls matched for sex and age. These changes mainly consisted of a reduction in CV, CT and folding in the frontal regions with extension in terms of CV to the cingulate gyrus, the temporal and parietal lobes.

Frontal lobes showed the most important structural changes in the three parameters suggesting that this region is of particular importance in EMAS; this is in line with signal changes in premotor cortex and supplementary motor area found in a previous EEG-fMRI study (Moeller et al., 2014). Cortical volume is a product of both CT and surface area. Cortical thickness is determined by the number of neurons within cortical columns (Fjell et al., 2015). Neuronal genesis being restricted to prenatal and perinatal life, reduced CT may thus be the result of alterations at the levels of synapses, dendrites and spines or changing myelination at the gray/white matter interface (Storsve et al., 2014). Local GI, a function of sulcal depth and gyral width, refers to gyral and sulcal formations, a prenatal process with relative lifetime stability. Thus, the latter can be considered as a more sensitive indicator of aberrant prenatal development (Mutlu et al., 2013). Atypical gyrification patterns were reported in several neurodevelopmental disorders (Fahim et al., 2012; Wallace et al., 2013). Our results raise the question whether alterations in CT and LGI are preexistent or are a consequence of sustained epilepsy and ASMs. Lower frontal volume has been shown in drug naïve patients with new-onset IGE, suggesting the existence of cortical morphology changes prior to epilepsy onset, and thus supporting the existence of genetically determined abnormal neuronal networks in generalized childhood epilepsy syndrome Wallace et al., 2013; Pulsipher et al., 2011).

The second important finding was a significant cerebellar volume reduction in our patients compared to controls. Cerebellar involvement was also shown by a fMRI study in EMAS supporting the hypothesis that a complex network involving the sensorimotor cortex, the putamen, the thalamus and the cerebellum may be involved in the generation of the motor seizures seen in this syndrome (Moeller et al., 2014). Cerebellar

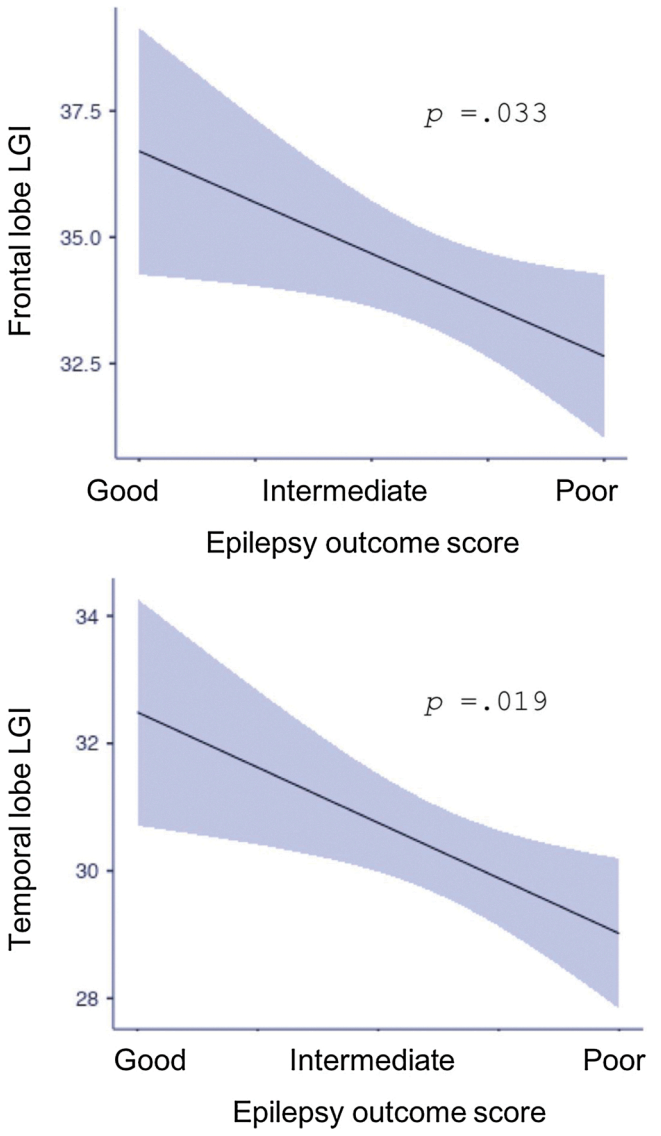


**Fig. 2.** Relation between frontal and temporal LGI and epilepsy outcomes as computed through regression analysis.

atrophy is a common finding in adults with chronic epilepsy and correlates to a longer duration of epilepsy or prolonged use of phenytoin (Lawson et al., 2000). In our cohort, reduced cerebellar volume seemed not related to epilepsy duration or number of ASM, even if no patients ever received phenytoin. However, they all had numerous ASMs for several years including benzodiazepines and lamotrigine, two medications with potential cerebellar toxicity (van Gaalen et al., 2014). Hence, we cannot rule out a mild negative impact of ASMs on the cerebellum but one can also postulate an independent alteration in its pre- and postnatal development.

We hypothesized that EMAS and IGE shared similar abnormal cortical sub-cortical networks because of shared seizure types. This is supported by the finding of reduced overall brain volume with reduced gray matter and preserved white matter in our cohort and in patients with IGE (Nuyts et al., 2017). Our findings of significant prominent structural alterations in the frontal lobes and the cerebellar volume reduction are also in line with EEG triggered fMRI studies in IGE patients that indicated frontal cortex, cerebellum and thalamus activation associated with generalized spike and waves discharges. Decreased gray matter volume in the cerebellum was reported in juvenile myoclonic epilepsy (Zhong et al., 2018); a diffusion tensor imaging studies in 15 adults and children with IGE showed structural cerebellar abnormalities by a decreased connectivity suggesting loss of cerebellar white matter integrity (Li et al., 2010). Although structural and functional alterations in the basal ganglia and thalamus were reported in IGE and EMAS, we did not find any abnormalities in these regions in our study (Moeller et al., 2014; Whelan et al., 2018).

Even though our morphometric study supports that EMAS and IGE share similar network abnormalities there are important clinical differences especially in age of onset, seizure frequency, cognitive outcomes and response to treatment that are not accounted for by these findings. Distinctive features may be captured only by studies combining ultra-high field MRI and functional imaging allowing quantitative comparisons between patients with EMAS, the different subtypes of IGE and controls.

Regarding the relation between the cognitive features of EMAS patients and morphometric findings, the widespread pattern of decreased cortical volume and thickness might be associated to a lower median IQ found in our cohort compared to the matched healthy controls. Correlations between cortical volume and thickness and neurocognitive deficits have previously been reported in focal and generalized epilepsies (Park et al., 2018; Tosun et al., 2004). Frontal alterations may underlie the executive, attentional and language deficits frequently seen in EMAS, even in patients with a better outcome (Filippini et al., 2006); together with the cerebellar involvement they may also contribute to the poor gross and fine motor skills that can also persist after the active phase of the epilepsy.

Via linear regression analyses, we explored how morphometric measures were quantitatively related to epilepsy and cognitive variables. We observed that patients with: i) late epilepsy-onset showed lower CV, and higher LGI; ii) poor outcome had lower LGI, and iii) higher number of ASM had relatively thicker cortex. These finding are unexpected and difficult to explain in our small cohort; looking back our data, children with later onset were not necessarily less severe in terms of seizure frequency, epilepsy duration or refractoriness, so that this variable is perhaps not meaningful. Regarding the higher number of ASM and relatively thicker cortex, which is also surprising, we have to precise that the number of ASM corresponded to the number of drugs taken at the moment of brain imaging, done at different ages. Therefore, this may not reflect the true burden of drug intake over time. Due to the small sample size, we did not measure interaction between duration of epilepsy and number of ASM which may be more meaningful in terms of impact on cortical development. (Wang et al., 2019).

We found that LGI was related to outcome groups, in the sense that lower LGI in our patient group was driven by the patients with poorer outcome, whereas patients with better outcome had normal LGI, similar to controls. Changes in LGI have been shown in cortical development abnormalities (Lenge et al., 2018), thus, this correlation may support the hypothesis of cortical microdysgenesis in EMAS patients with poorer outcomes raised by Inoue et al. (Inoue et al., 2014).

No correlations emerged for cortical and cerebellar volumes. Duration of epilepsy did not predict any morphometrics measures as reported in IGE (Bernhardt et al., 2009; Tosun et al., 2011).

With regard to the population studied, the clinical outcomes were in line with previous studies on EMAS reporting 20–35% of children with borderline IQ or intellectual disability +/- refractory epilepsy few years after seizure onset. At last, median IQ was lowered as previously reported in largest cohort (Oguni et al., 2002; Filippini et al., 2006; Kaminska and Oguni, 2013). Our cohort is therefore representative of this rare epilepsy syndrome. However, our study has several limitations. First, it is retrospective and our sample is small, heterogeneous in age, severity, disease duration and ASM regimen. Second, the low number of patients did not allow detailed morphometric sulcal/gyral analyses in different brain regions and especially in frontal lobes, or interaction terms in the linear regression analyses. Finally, EMAS is an electro-clinical syndrome with a complex genetic basis that may be different from one patient to another; it is likely that our cohort includes

patients with different genetic causes with variable impact on brain development.

## 5. Conclusion

Advanced structural imaging techniques allowed to show the presence of significant cortical changes in EMAS, partially related to epilepsy and cognitive variables. Whether these changes reflect genetically determined abnormal morphometries or are a consequence of the active epilepsy remains to be solved. A longitudinal prospective study is needed to clarify these issues taken into account the ethical and methodological limitations inherent to the rarity of EMAS, the young age of onset and the high seizure frequency often requiring multiple ASMs.

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## Declaration of Competing Interest

The authors report no declarations of interest.

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We would like to thank all participating family members.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2021.106771.

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