Epilepsy & Behavior 91 (2019) 68–74

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

# Age-related MR characteristics in mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy (MOGHE)

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ARTICLE INFO

*Article history:*
Revised 29 June 2018
Accepted 8 July 2018
Available online 27 July 2018

*Keywords:*
MOGHE
MRI
Epilepsy
Malformation of cortical development
Oligodendroglia
Oligodendroglial hyperplasia

ABSTRACT

*Background:* Mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy (MOGHE) is a newly described, rare histopathologic entity detected in resected brain tissue of patients with refractory epilepsies. It shows a predominantly frontal localization causing a difficult-to-treat epilepsy with onset usually in early childhood. Histologically, MOGHE is characterized by blurred gray–white-matter boundaries with increased numbers of heterotopic neurons in the subcortical white matter and increased density of oligodendroglia. Little is known, to date, about radiologic features of MOGHE. Here, we report typical and age-related magnetic resonance (MR) characteristics of MOGHE.
*Patients and methods:* Retrospective analysis of 40 preoperative MR images of 25 pediatric patients with MOGHE (m/f: 13/12) who underwent epilepsy surgery at a median age of 9.3 years at our center between 2003 and 2018. Median age at magnetic resonance imaging (MRI) was 5.2 years (1.5–20.7 years).
*Results:* Two MR subtypes were found: subtype I with an increased laminar T2 and fluid attenuated inversion recovery (FLAIR) signal at the corticomedullary junction and subtype II with reduced corticomedullary differentiation because of increased signal of the adjacent white matter. Distribution of subtypes was age-related, with subtype I occurring between 1.5 and 5.1 years (median 2.6 years) and subtype II between 3.4 and 20.7 years (median 14.1 years). In one patient, MRI at the age of 2.7 years showed subtype I but had converted to subtype II by the age of 16 years. Histology revealed that in addition to the above mentioned typical findings of MOGHE, patchy areas of reduced density of myelin in 6 of 7 patients presenting subtype I out of 14 patients in which retrospective analysis regarding myelination was accessible.
*Conclusion:* Magnetic resonance characteristics in patients with MOGHE are age-related and seem to change from subtype I to subtype II probably because of maturational processes between 3 and 6 years. Patchy areas of hypomyelination in histology seem to disappear during brain maturation and may therefore represent the histologic correlate of laminar T2 and FLAIR hyperintensities in subtype I.
**This article is part of the Special Issue "Individualized Epilepsy Management: Medicines, Surgery and Beyond".**



## 1. Introduction

Mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE) is a new histopathologic entity described in patients with difficult-to-treat frontal lobe epilepsy in 2017 by Schurr and Coras [1, 2]. They reviewed 52 cases, originally reported as histologically nonlesional submitted from various epilepsy centers. In 22 cases, a distinct histological phenotype with "*blurred gray–white-matter boundaries due to heterotopic neurons in white matter and increased numbers of subcortical oligodendroglial cells*" was found [1]. A subset of

*Abbreviations:* FCD, focal cortical dysplasia; FLAIR, fluid attenuated inversion recovery; hrMRI, high resolution magnetic resonance imaging; mMCD, mild malformation of cortical development; MPRAGE, magnetization-prepared rapid gradient echo; MRI, Magnetic resonance imaging; OPC, oligodendrocyte precursor cell; PDGFRa, platelet-derived growth factor receptor alpha; POGHE, proliferative oligodendroglial hyperplasia and epilepsy.

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https://doi.org/10.1016/j.yebeh.2018.07.009
1525-5050/

oligodendroglial cells was platelet-derived growth factor receptor (PDGFR)-alpha immune-reactive, a marker for putative oligodendroglial precursor cells (OPC) indicating early maturational stages of the oligodendroglial lineage [3, 4]. These cells showed increased proliferative activity indicated by nuclear Ki-67 labeling. NeuN immunohistochemistry revealed a normal six-layered cortical architecture, neither dyslamination, dysmorphic neurons, nor balloon cells were detected. Without histological hallmarks for cortical dysplasia [5] this entity was provisionally classified as mild malformation of cortical development (mMCD) because of the blurred gray–white-matter boundaries and increased numbers of heterotopic neurons [6] in the deep cortical layers and white matter.

Perivascular clustering of oligodendrocytes is well-known in specimen obtained from surgery of patients with temporal lobe epilepsies [7–9]. These findings originally named reactive astrogliosis or oligodendrogliosis are histopathologically distinct from MOGHE regarding the distribution of oligodendroglial cells and their proliferative activity [1].

The histologic pattern of MOGHE in brain specimen of patients with epilepsy was first described in 2002 as oligodendroglial hyperplasia by Burger [10]. In 2009, Nesbit and Hamilton presented a case with similar histology together with the first description of magnetic resonance imaging (MRI) abnormalities in this entity with blurring of the corticomedullary differentiation [11]. In 2013, Coras et al. renamed this entity into proliferative oligodendroglial hyperplasia with epilepsy (POGHE) because of their findings of increased proliferative activity of oligodendroglia [12]. In 2014, magnetic resonance (MR) features of 5 patients with MOGHE (4 to 23 years old) were described by Woermann et al. [13] with blurred, not sharply demarcated gray–white matter interface in all 5 and thickened cortex in three patients. They did not report circumscribed fluid attenuated inversion recovery (FLAIR) or T2 hyperintensities. The authors concluded that, despite significant differences in the cellular composition, MR features of MOGHE were similar to MR features of focal cortical dysplasia (FCD). Magnetic resonance imaging in several pediatric patients with MOGHE treated in our center, however, revealed laminar subcortical hyperintensities in FLAIR and T2, which were different from typical MR features of FCD. In order to specify these marked hyperintensities as characteristic or even specific MR features for this entity, all MRIs of patients with MOGHE from our center were reviewed.

## 2. Patients and methods

### 2.1. Patients

Our study included all 25 patients (m/f: 13/12) who were diagnosed as MOGHE and underwent epilepsy surgery in our center between 2003 and 2018. Written informed consent for this retrospective data analysis was obtained from all patients/caretakers.

Before 2012, when the histological hallmarks of MOGHE were not widely known, 5 patients were classified as FCD type I; 5 patients as mMCD; in two patients, the only pathology described was reactive astrogliosis; one patient showed a reduced differentiation of gray and white matter with glial hyperplasia. From 2012 up to 2018, 7 patients were primary classified as MOGHE based on the above-mentioned criteria, 5 patients were classified as mMCD with (oligodendro)glial hyperplasia. All of the patients' epilepsies were medically refractory following the 2010 International League Against Epilepsy definition [14]. Median age of onset of epilepsy was 2.3 years (0.4–13 years). Presurgical evaluation encompassed long-term video-electroencephalography (EEG) monitoring for 7 days in all cases, invasive recordings with subdural grids and strips in 5 cases, and stereo-EEG in 3 cases. Localization of the epileptogenic zone was frontal in 13/25 cases, hemispheric in 8/25 cases, temporooccipital in 2/25 cases, and 1/25 cases each frontotemporal and temporal. Lateralization of the epilepsy was left-sided in 15 and right-sided in 10 patients. Postoperative seizure control was assessed according to Engel classification [15], with 13/25 Engel class 1, 3/25 Engel class 2, 5/25 Engel class 3, and 2/25 Engel class 4; outcome data were not available in one patient and pending in another. (See Table 1.)

### 2.2. Methods

All patients underwent at least one high-resolution cranial MRI under general anesthesia as part of the presurgical evaluation. Magnetic resonance imaging was performed on a 1.5-T whole body scanner in our center (Siemens MAGNETOM Symphony TIM, Siemens Medical Solutions, Erlangen, Germany) or in the institute for radiology, Olga hospital Stuttgart (Siemens MAGNETOM Avanto, Siemens Medical Solutions, Erlangen, Germany), with a 12-element head coil (used as 4-channel coil) in both centers. The 3D T2 sampling perfection with application optimized contrasts using different flip angle evolutions (SPACE) and FLAIR SPACE sequences were acquired with an isotropic spatial resolution of 0.6 $mm^3$ (T2) and $0.4 \times 0.4 \times 1.2$ mm (FLAIR), as part of our high-resolution epilepsy protocol. Total acquisition times were 1 h 10 min and 38 min, respectively.

All preoperative MRIs were reviewed on a dedicated workstation (IMPAX EE, Agfa HealthCare NV, Belgium) by a pediatric radiologist (PW) with special expertise in pediatric neuroradiology and imaging characteristics of epileptogenic lesions and a neuropediatrician (TH) with several years of training in the field of MRI evaluation in patients with severe epilepsies. Both readers were aware of electroclinical data and that all patients had histologically confirmed MOGHE, according to the methods used by Schurr et al. [1]. Written informed consent was obtained from all patients/caretakers, no ethics committee approval was needed due to retrospective data analysis, without any influence an therapeutic decisions.

## 3. Results

Two distinct MR subtypes in patients with MOGHE could be defined. Subtype I is characterized by increased laminar T2 and FLAIR signal at the corticomedullary junction (Fig. 1) and subtype II by reduced corticomedullary differentiation because of increased signal of the adjacent white matter (Fig. 2). One patient did not match these radiologic criteria and was therefore excluded from further analysis.

Interestingly, the distribution of subtypes was age-related, with subtype I occurring between 1.5 and 5.1 years (median 2.6 years) (10 MRIs) and subtype II between 3.4 and 20.7 years (median 14.1 years) (14 MRIs) (Fig. 3).

In one patient, MRI at the age of 2.7 years showed subtype I and had changed to subtype II by the age of 16 years (Fig. 4). In another patient with 2 MRIs between 1.6 and 2.9 years, a reduction of subcortical laminar hyperintensities was observed between these studies (Fig. 5). In concordance with the histological findings in brain specimen of patients with MOGHE as described by Schurr et al. [1], patchy areas of reduced density of myelin were found in 6 out of 7 patients presenting subtype I in the last MRI before surgery out of 14 patients in which retrospective data regarding myelination were accessible.

## 4. Discussion

Magnetic resonance patterns in patients with MOGHE are age-related, with subtype I characterized by laminar signal hyperintensities and predominance in young patients with a median age of 2.6 years and subtype II with appearance in the older age group, median age 14.1 years, with reduced corticomedullary differentiation.

Laminar hyperintensities in T2 and FLAIR sequences as hallmarks for subtype I are not exclusively seen in patients with MOGHE.

**Table 1**
Patients included in this study.
Abbrev.: f = female; m = male; MRI = magnetic resonance imaging; mMCD = mild malformation of cortical development;
FCD = focal cortical dysplasia; res. = resection; disc. = disconnection; red. diff. = reduced differentiation, pend. = pending; n.a. = not available
P22 had undergone two operations marked with 1. and 2.
Outcome data were not available in P13 and pending in P1.

| Patient ID | Gender | Localization | Lateralization | Onset of epilepsy (years) | Duration of epilepsy (years) | Age at surgery (years) | Age at MRI | Presumptive etiology (MRI) | Type of surgery | Initial histology | Histology reclassified | MOGHE subtype (MRI) | Outcome (Engel) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P1 | f | frontal | left | 6.3 | 2.2 | 8.5 | 7.5 | FCD | lesionectomy | MOGHE | MOGHE | 2 | pend. |
| P2 | m | frontal | right | 1.2 | 15.7 | 16.9 | 2.7 | FCD | subtotal frontal res. | MOGHE | MOGHE | 2 | 1a |
| P3 | f | hemispheric | left | 0.4 | 3.3 | 3.7 | 2.1 | MOGHE | subtotal hemispherectomy | MOGHE | MOGHE | 1 | 1a |
| P4 | m | hemispheric | left | 0.5 | 4.9 | 5.4 | 5.0 | FCD I | hemispherotomy | MOGHE | MOGHE | 1 | 2a |
| P5 | f | frontal | right | 1.2 | 0.4 | 1.6 | 1.5 | MOGHE | subtotal frontal res. | MOGHE | MOGHE | 1 | 1a |
| P6 | f | frontal | left | 5 | 5.5 | 10.5 | 9.1 | FCD I | subtotal res. + temporal anterior res. | MOGHE | MOGHE | 2 | 2a |
| P7 | f | frontal | right | 3.8 | 10.7 | 14.5 | 12.9 | FCD | lesionectomy | MOGHE | MOGHE | 1 | 1a |
| P8 | m | frontal | right | 0.8 | 1.8 | 2.6 | 2.4 | FCD | subtotal frontal res. | mMCD + (oligodendro)glial hyperplasia | MOGHE | 1 | 1a |
| P9 | m | frontal | left | 2 | 21.9 | 23.9 | 13.3 | FCD I | subtotal res. + temporal anterior res. | mMCD + (oligodendro)glial hyperplasia | MOGHE | 2 | 1a |
| P10 | f | frontal | right | 0.6 | 2.9 | 3.5 | 2.6 | FCD | subtotal frontal res. | mMCD + (oligodendro)glial hyperplasia | MOGHE | 1 | 1a |
| P11 | m | frontal | left | 0.5 | 2.8 | 3.3 | 2.6 | FCD | subtotal frontal res. | mMCD + (oligodendro)glial hyperplasia | MOGHE | 1 | 1a |
| P12 | m | frontal | left | 0.5 | 3.9 | 4.4 | 3.4 | FCD | lesionectomy | mMCD + glial hyperplasia | MOGHE | 2 | 1a |
| P13 | f | frontal | right | 0.4 | 4.9 | 5.3 | 3.8 | FCD | subtotal frontal res. | mMCD II | MOGHE | 2 | n.a. |
| P14 | m | frontal | left | 1.5 | 15.9 | 17.4 | 15.9 | FCD | subtotal frontal res. | mMCD + glial hyperplasia | MOGHE | 2 | 3a |
| P15 | m | temporooccipital | left | 0.6 | 3.8 | 4.4 | 3.8 | FCD | temp. res. + occipital disc. | red. diff. of gray/white matter + glial hyperplasia | MOGHE | 2 | 4a |
| P16 | m | hemispheric | left | 2.5 | 2.3 | 4.8 | 3.0 | FCD I | hemispherotomy | mMCD II | MOGHE | 1 | 1a |
| P17 | f | temporooccipital | left | 0.5 | 2.1 | 2.6 | 1.5 | FCD | subtotal frontal + temporal res. + parietooccipital disc. | FCD Ia | MOGHE | 1 | 2b |
| P18 | f | hemispheric | right | 0.5 | 1.6 | 2.1 | 1.9 | FCD | subtotal hemispherectomy | FCD I | MOGHE | 1 | 3a |
| P19 | f | hemispheric | left | 0.4 | 10.2 | 10.6 | 9.5 | FCD | subtotal frontal res. | FCD I | MOGHE | 2 | 4a |
| P20 | f | frontotemporal | left | 1 | 2.2 | 3.2 | 1.6 | FCD I | subtotal hemispherectomy | FCD I | MOGHE | 1 | 1a |
| P21 | m | hemispheric | right | 2.3 | 13.6 | 15.9 | 12.1 | FCD | subtotal hemispherectomy | mMCD II | MOGHE | 2 | 3a |
| P22 | m | hemispheric | right | 6 | 9.3 | 15.3 | 11.7 | FCD | 1. parietooccipital res. 2. subtotal frontal res. | reactive astrogliosis | MOGHE | 2 | 3a |
| P23 | m | frontal | left | 13 | 5.0 | 18.0 | 13.8 | FCD | subtotal frontal res. | mMCD II | MOGHE | 2 | 1a |
| P24 | m | temporal | left | 5 | 11.3 | 16.3 | 15.3 | FCD | temporal anterior res. | reactive astrogliosis | MOGHE | 2 | 1b |
| P25 | f | hemispheric | right | 0.9 | 17.8 | 18.7 | 17.5 | FCD | subtotal frontal res. | FCD Ia | MOGHE | 2 | 3a |

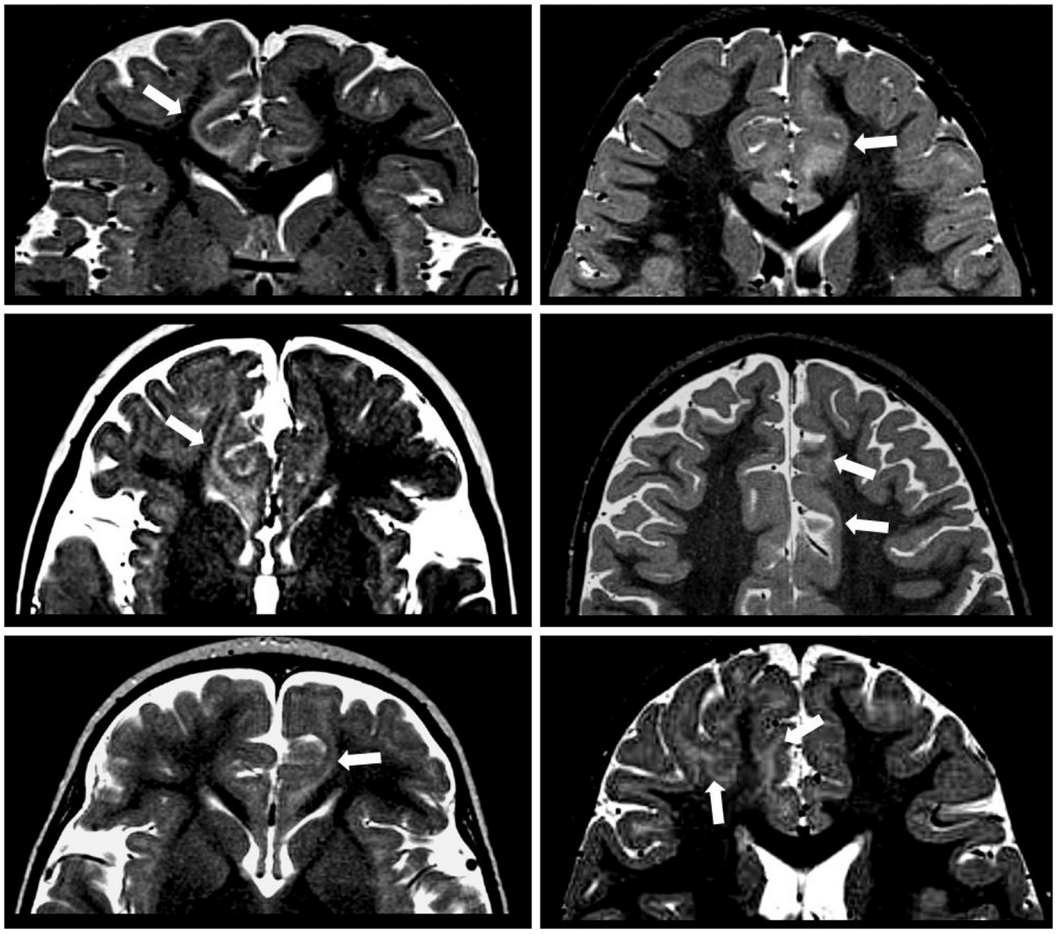

**Fig. 1.** Axial T2-weighted MRI of 6 patients with subtype I in the frontal lobe. Arrows mark increased laminar T2 signal at the corticomedullary junction as radiological hallmark.

Frontal and temporal lobes in healthy toddlers and young children are exhibiting a more protracted myelination compared with other parts of the developing human brain [16]. This "physiologic delay" of normal myelination, predominantly seen in the first 4 years of life, is characterized by laminar subcortical hyperintensities too. In contrast to the findings in MOGHE, these normal hyperintensities can be found bilaterally but less prominent and in significantly younger children (Fig. 6).

Because of the similarity of radiologic features of MOGHE subtype I with the "physiologic" protracted myelination in young children, we suppose that impaired or delayed myelination is the radiologic correlate of MOGHE subtype I.

Retrospective data of patchy areas of reduced density of myelin in 6 out of 7 patients presenting subtype I out of 14 patients in which retrospective data regarding myelination were accessible support this hypothesis (Fig. 7).

Myelination of the human brain follows a complex and precisely timed program [17] in which PDGFR-alpha immuno-reactive OPC differentiate into mature oligodendrocytes to produce the insulating sheath of axons [18]. In MOGHE, high density of proliferative PDGFR-alpha immuno-reactive oligodendrocyte precursor cells and patchy areas of reduced density of myelin can be found in the white matter, indicating a disturbance in this maturational process [2]. Whether this OPC proliferation is a secondary regenerative phenomenon due to an impairment of oligodendroglial maturation with reduced density of myelin or the primary pathologic cause for this entity is to date unclear and has to be elucidated in further studies.

Magnetic resonance subtypes in MOGHE are not static but seem to convert from subtype I to subtype II during brain development between the age of 3 to 5 years. We assume that at one time point oligodendroglial precursor cells seem to overcome the maturational arrest and differentiate to some extent into mature myelinating oligodendrocytes. As myelination progresses a decline of laminar hyperintensities can be observed, as seen in one patient, leading to a complete conversion from subtype I to subtype II, as seen in another patient.

Magnetic resonance characteristics of subtype II with reduced corticomedullary differentiation because of increased signal of the adjacent white matter are subtle in comparison to subtype I, therefore detection of this type of MOGHE is more difficult. During the conversion from subtype I to subtype II a portion of OPCs differentiate into mature, myelinating oligodendrocytes. The remnants of the early OPC proliferation can still be found in the subcortical white matter and deep cortical layers. We assume that these cells, together with heterotopic neurons [19], are responsible for the increased white matter signal and thus for reduced corticomedullary differentiation and represent the histologic correlate for MR features in subtype of MOGHE.

An increase in white matter signal in T2 and FLAIR sequences with reduced corticomedullary differentiation can also be found in patients with FCDs [5, 6, 20], predominantly FCD type II, which have to be considered as possible differential diagnosis to MOGHE subtype II.

In FCD type IIb, white matter changes are more circumscribed with a transmantle-like appearance and accompanied by signal abnormalities of the cortex [19] appearing mostly as signal decrease in T2-weighted images and increased cortical thickness, and therefore, can easily be differentiated from MOGHE subtype II [20]. Differentiation of FCD type IIa from MOGHE subtype II can be challenging with widespread MR abnormalities and predominantly blurred corticomedullary

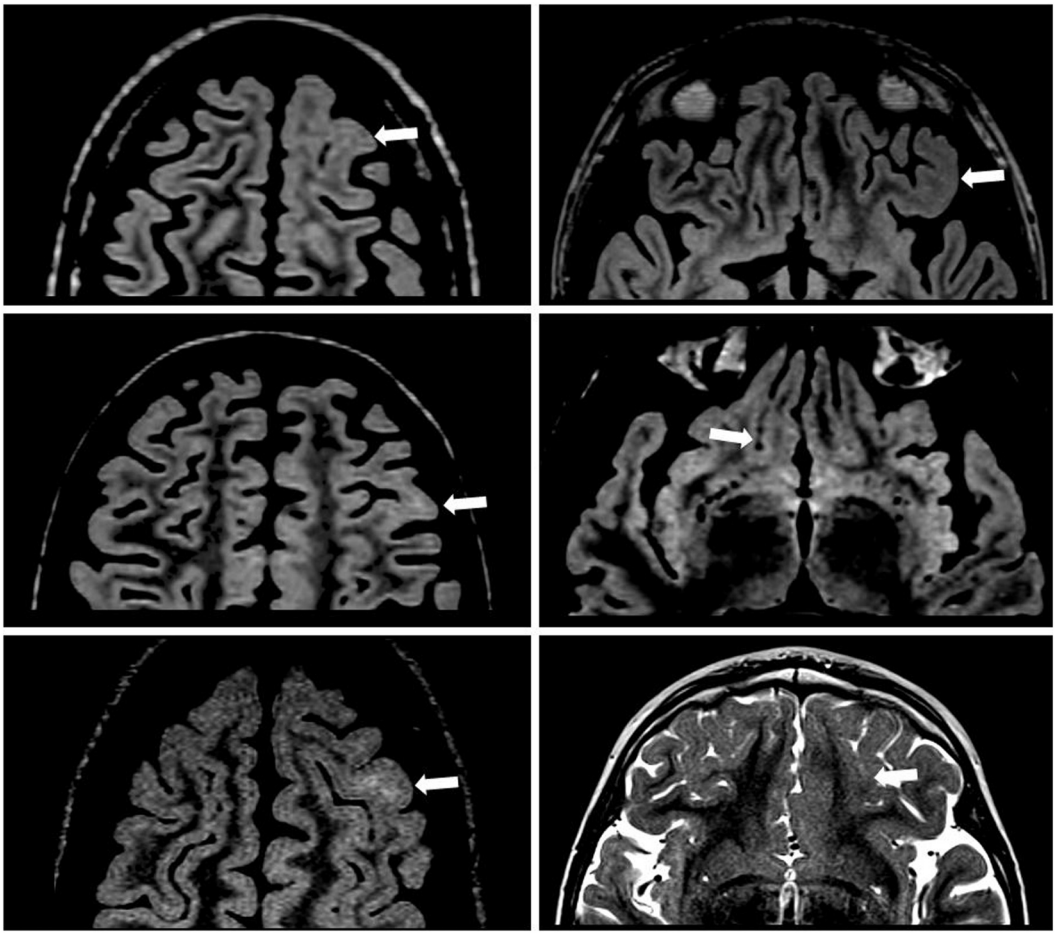

**Fig. 2.** Axial FLAIR (images 1–5) and T2-weighted MRI (image 6) of 6 patients with subtype II in the frontal lobe. Arrows mark reduced corticomedullary differentiation because of increased signal of the adjacent white matter.

differentiation as seen in MOGHE [21]. Increased cortical signal in FLAIR, cortical thickening, and abnormal gyral and sulcal patterns can help to differentiate FCD type IIa from MOGHE subtype II but are not always present in these cases [19] (Fig. 8).

Magnetic resonance abnormalities in FCD type Ia classified according to Blümcke et al. [5] are subtle and widespread, consisting of slightly increased white matter signal in T2- and FLAIR-weighted images and a reduction of volume of the white matter of the affected areas [22]. Focal cortical dysplasia type Ib and Ic are rarely seen at our center.

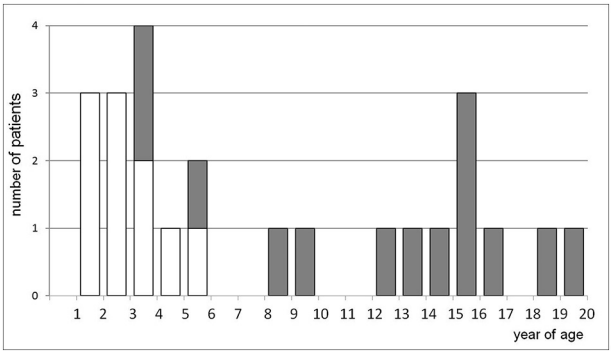


**Fig. 3.** MOGHE subtypes according to patient age (in years). Note the age-related distribution of subtype I (white) up to 5 years and subtype II (gray) from 3 years up to 20 years.

Therefore, FCD type IIa has to be considered as the most likely differential diagnosis to the MOGHE subtype II.

Admittedly, our study has several shortcomings: Sensitivity and specificity of laminar hyperintensities as described in this study for the radiologic diagnosis of MOGHE subtype II needs to be elucidated in future studies. A blinded approach with further blinded, experienced neuroradiologists in order to prove the observations of this pilot study is necessary. Differential diagnosis of epileptogenic lesions such as FCD type I, FCD IIa/b, and mMCD will be included in this approach.

Because experienced neuroradiologists and epileptologists were not aware of this MR pattern it seems to be unlikely a common and unspecific finding in this age group.

Actual frequency of MOGHE in our collective cannot be estimated correctly because several cases before 2012 might have been misdiagnosed as FCD or mMCD II in the lack of knowledge of MOGHE specific histological and radiological hallmarks.

## 5. Conclusion

Mild malformation of cortical development with oligodendroglial hyperplasia and epilepsy or MOGHE is a new, not yet widely recognized neuropathological entity, associated with severe epilepsies in childhood. We were able to distinguish 2 specific, age-related MR subtypes in patients with MOGHE. Here we first describe laminar T2 and FLAIR hyperintensities as radiological hallmark for subtype I. Knowledge of these MR characteristics and their age-related conversion from MOGHE subtype I to subtype II between the ages of 3 to 5 years is crucial for the diagnosis of this new challenging entity. As preliminary data regarding postoperative seizure outcome of patients operated before and after

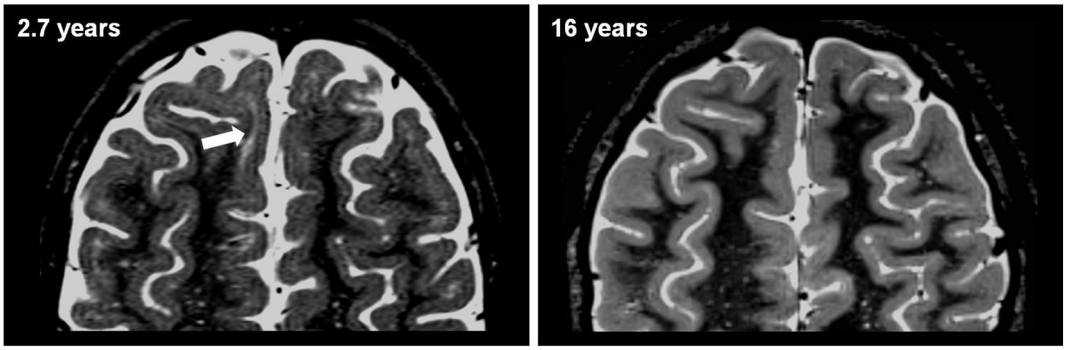


**Fig. 4.** Axial T2-weighted MRI of one patient with subtype I at the age of 2.7 years (left) and subtype II at the age of 16 years (right). Note increased laminar T2 signal at the corticomedullary junction (arrow) in subtype I (left) that was no longer detectable in subtype II (right).

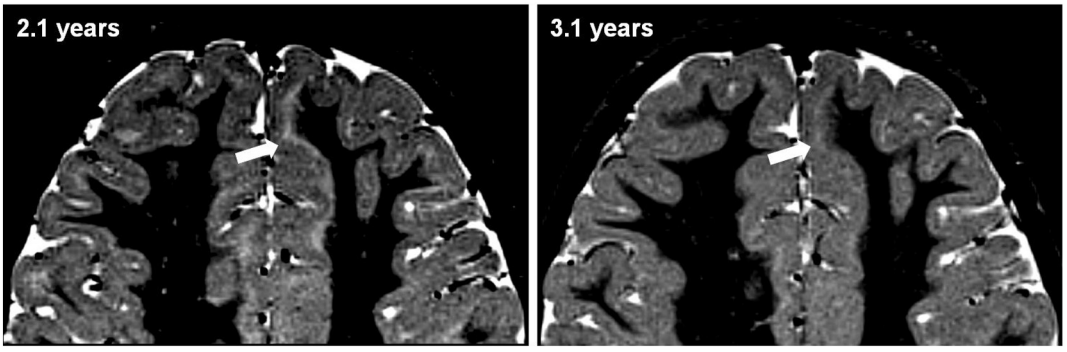


**Fig. 5.** Axial T2-weighted MRI of one patient with subtype I at the age of 2.1 years (left) and 3.1 years (right). Note the marked laminar hyperintensities at the age of 2.1 years and the decline of these findings at the age of 3.1 years.

2012 refer to significantly higher rates of seizure freedom in patients operated after 2012, we suppose that being aware of this new entity during presurgical evaluation might have an impact on surgical strategy, extent of resection, and hence, postoperative outcome. Outcome seems to be more favorable following extended resections rather tailored lesionectomies because clear delineation of the epileptogenic lesion in both subtypes in MRI can be difficult [1].

## Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Author contribution

TH, MK, and MS drafted the manuscript. Data analysis was performed by TH. PW and TH reviewed the MRIs. PW, TP, and HH revised the manuscript. IB and RC performed histological analysis and revised the manuscript. All authors gave their approval to the final version of this paper.

## Conflict of interest

None of the authors has any conflict of interest to disclose that is related to the content of this study.

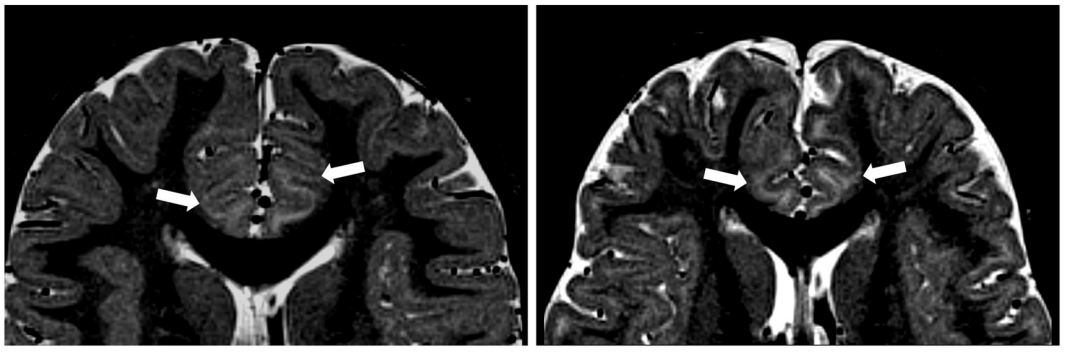

**Fig. 6.** Axial T2-weighted MRI of two healthy children at the age of 14 and 18 months with increased bilateral laminar T2 signal at the corticomedullary junction frontal mesial (arrow) as a sign of "physiologic delay" of normal myelination.

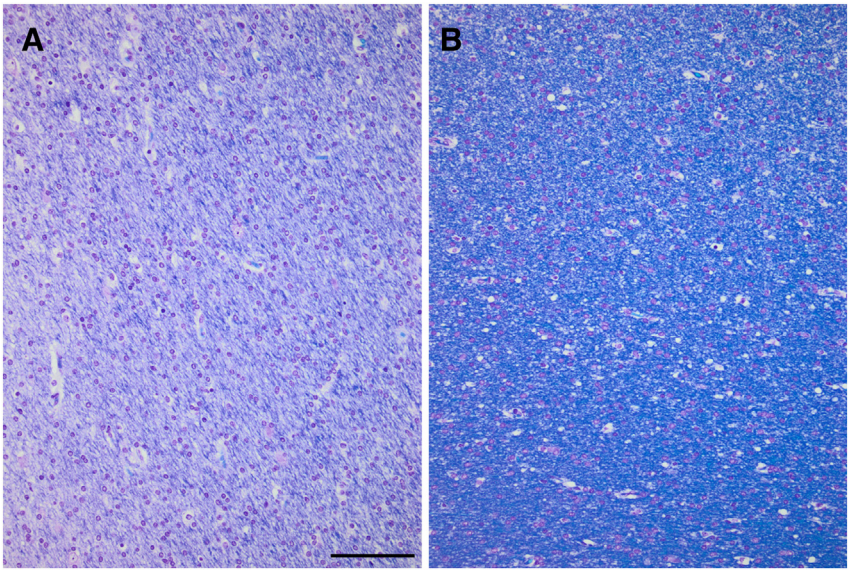


**Fig. 7.** Nissl-Luxol-fast-blue histochemistry (A & B) shows areas of reduced density of myelin in patient 5 with MOGHE subtype I (A). In contrast, regular myelination in patient 6 with MOGHE subtype II (B). (Scale bar in A: 100 μm, applies also for B).

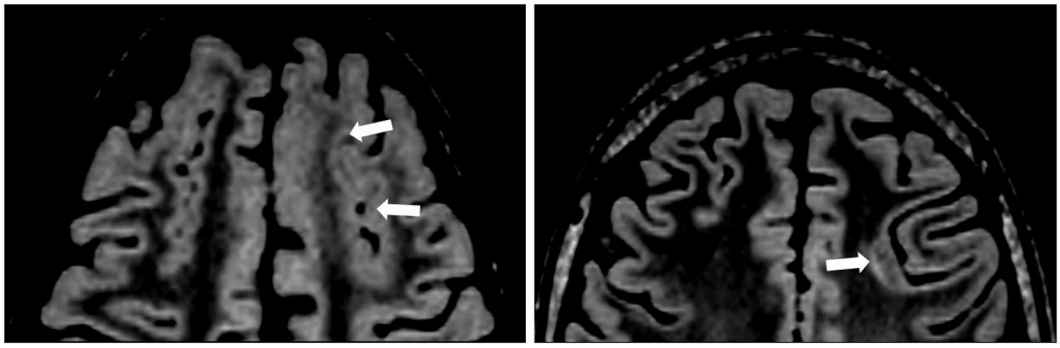

**Fig. 8.** Axial FLAIR-weighted MRI of 2 patients with FCD type IIa in left frontal lobe. Arrows mark reduced corticomedullary differentiation (left) and increased cortical signal (right) as radiological hallmarks for FCD type IIa as differential diagnosis to MOGHE subtype II.

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