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Age-dependent semiology of frontal lobe seizures

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ABSTRACT

Introduction: Frontal lobe epilepsy is the second most frequent origin of focal epilepsy. Various studies have discussed localizing aspects of ictal signs in frontal lobe epilepsy; the effect of age on semiological manifestations has, however, not been analyzed so far.

Material and methods: We retrospectively analyzed video-documented semiological signs in a cohort of 122 consecutive patients aged 0–70 years (mean age: 24.9 years) with EEG/MR evidence for frontal lobe epilepsy undergoing video-EEG telemetry assessment between 1999 und 2016.

Results: In this patient cohort, most common etiologies were focal cortical dysplasia (48%) and tumors (16%). Most frequent ictal manifestations overall were impaired language comprehension (60.3%), unilateral tonic posturing (58.9%), unilateral cloni (46.6%), versive movements (44.5%), vocalization (42.5%) and impaired reactivity to non-verbal stimuli (40.4%). With increasing age, sign of four ($p = 0.019$), dystonic posturing ($p = 0.026$), changes in heart rate ($p = 0.014$) and impaired reactivity to non-verbal stimuli ($p = 0.009$) occurred significantly more frequently. In contrast, myoclonic components were significantly less frequent observed in the higher age group ($p = 0.037$).

Conclusions: Frontal lobe seizures can be categorized into different behavioral manifestations related to involved symptomatic brain regions, including clonic, bilateral asymmetric tonic seizures and complex motor phenomena. In this cross-sectional study, we found age-related changes in the frequency of both, motor and non-motor semiological elements. Especially simple lateralized motor signs like dystonic posturing, sign of four and version were more common with increasing age. Age-dependent alterations in phenomenology may reflect maturation in connectivity and seizure propagation within and beyond the frontal lobe, and affect the localizing and lateralizing value of ictal phenomena.

1. Introduction

About 25% of patients with refractory focal epilepsy are diagnosed with frontal lobe epilepsy (FLE) (Beleza and Pinho, 2011). Although it is ranked as the second most common focal epilepsy type after temporal lobe epilepsy and manifests from early childhood to seniority, the age-dependent development of its semiological manifestation has not been well characterized. Hypermotor, unilateral clonic and tonic asymmetric movements are considered typical elements of frontal lobe semiology (Beleza and Pinho, 2011). Several semiological studies discuss localizing and lateralizing aspects in FLE (Bonelli et al., 2007; Bonini et al., 2014; Jobst et al., 2000). The specificity of semiological signs in terms of localization, however, depends critically on the connectivity within and beyond the frontal lobe and its maturation during life. Clinical semiology and its sequential expression depend upon multifactorial aspects. Thus, it reflects the dynamic interaction between anatomical origin of ictal discharge and the regions of propagation as determined by functional coupling within networks (Chauvel and McGonigal, 2014).

To our knowledge, there is little data so far on age-dependent manifestation of semiological elements. We here assess the impact of age on the evolution of semiological characteristics in a large patient cohort comprising both, children and adults.

2. Material and methods

Electronic clinical records of patients undergoing video-EEG telemetry for focus localization and syndrome diagnosis at the Epilepsy Center Freiburg, Germany were reviewed retrospectively for the time period of 1999–2016 for this cross-sectional study. Included were all patients diagnosed with frontal lobe epilepsy based on the presence of interictal and ictal video-EEG findings suggesting frontal lobe

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epileptogenesis, and in lesional patients a concordant MRI lesion (78% of patients). The analysis was based on long-term video-EEG recordings of 122 patients (60 male) with scalp electrodes placed according to the international 10–20 system and frequently additional closely spaced electrodes, or with intracranial electrodes. All patients undergo standardized testing during the ictal and postictal period including assessment of reactivity to verbal and non-verbal stimuli, verbal body commands, naming, reading, memorizing words and objects presented during the ictal phase. Repeated monitorings were counted separately if performed at intervals of more than one year, leading to 146 age-dependent data points. When the interval between recordings was less than one year, monitoring results were joined. Semiological elements and symptoms derived from the glossary of Blume et al. (2001). (Blume et al., 2001) were coded for a maximum of ten seizures per patient, lumped per individual and analyzed regarding age-dependent manifestation. The Blume glossary was chosen as it considers all semiological signs and symptoms as opposed to classifications which put emphasis on a predominant sign (Lüders et al., 1998) or on the initial sign only (Fisher et al., 2017a, 2017b). Semiological elements observed in less than 5 cases within the whole patient group were not included in the statistical analysis. To study age-dependent effects, binary logistic regression with age at time of monitoring as independent variable was applied. Patients were divided into different subgroups by age: 0–5 years (n1 = 9; 6.2%), 6–11 years (n2 = 20; 13.7%), 12–17 years (n3 = 27; 18.5%) and 18 years and older (n4 = 90; 61.6%).

3. Results

3.1. Demographics and baseline characteristic

Onset of epilepsy ranged between 0 and 56 years (mean: 9.4 years, earliest onset was during the first days of living), age at observation was 4 months to 70 years (mean: 24.9 years). At the time of video documentation, patients had been living with epilepsy for up to 50 years (mean: 15.5 years). Focal origin in the frontal lobe was based on imaging complemented by histology in patients undergoing surgical resection, and on interictal and ictal EEG patterns. Several patients underwent additional investigations as well, i.e. MEG (3%), PET (57%), SPECT (16%) and intracranial EEG (43%). 78% of patients had a MRI-visible lesion: most frequent etiologies were focal cortical dysplasia (48%) and low-grade tumors (16%) (for a complete list see Table 1). Surgical outcome one year after surgery was 59.3% Engel I (seizure free or remaining auras only), 18.7% Engel II (> 90% seizure reduction), 14.5% Engel III (> 75% seizure reduction) and 7.2% Engel IV (less than 75% seizure reduction).

3.2. Frequency of ictal semiology

The observed ictal semiological signs and their frequency are given in Table 2. Overall, most frequent semiological features were disturbed language comprehension (60.3%), unilateral tonic posturing (58.9%), unilateral cloni (46.6%), versive movements (44.5%), vocalization (42.5%) and disturbed reactivity to non-verbal stimuli (40.4%). Patients with ictal speech had right frontal epileptogenesis in 55%, left frontal in 27%; 18% of patients had no clear lateralization of seizure onset. Two patients with ictal aphasia both had a left frontal seizure origin. Overall, hyperkinetic seizures were witnessed in 16% of patients. Seizures were classified as hyperkinetic mainly by increased irregular sequential movement as kicking, pedaling, rocking and thrusting of the pelvic.

Impaired reactivity to non-verbal stimuli ($p = 0.009$), changes in heart rate ($p = 0.014$), sign of four ($p = 0.019$) and dystonic posturing ($p = 0.026$) were significantly more frequently observed with increasing age (Fig. 1). Some additional elements also tended to be more common with higher age: unilateral manual automatism ($p = 0.096$), unilateral dystonic posturing ($p = 0.060$), vocalization ($p = 0.079$), postictal aphasia ($p = 0.074$) and head version ($p = 0.056$). In contrast, myoclonic elements were witnessed significantly less often in adult patients aged 18 years and older ($p = 0.037$).

In our study population, an aura was reported by 20.5% of patients with FLE; areas were somatosensory (11%), epigastric (4.8%), cephalic (3.4%), affective in 2.7%, visual 2.1% or gustatory 0.7%. None of the patients experienced an auditory or olfactory aura. Patients in the age group below six years neither reported auras nor had unilateral dystonic posturing or postictal Todd's paresis. Sign of four was observed

Table 1
Incidence of etiology based on MRI and/or histology.

etiology		n	%
focal cortical dysplasia		58	47.5
	tuberosis sclerosis	*3*	*2.5*
tumors		19	15.6
	neurodevelopmental tumor	*7*	*5.7*
infection		3	2.5
posttraumatic		3	2.5
perinatal lesion		2	1.6
hemorrhage residual		2	1.6
cavernoma		2	1.6
focal cortical dysplasia or tumor		2	1.6
other		4	3.3
unknown		27	22.1
overall		122	100.0

Table 2
Frequency of ictal semiological features in the overall population.

semiological elements	%	semiological elements	%
aura	**20.5**	hyperkinetic	20.5
somatosensory	11.0	grimacing	7.5
epigastric	4.8	atonia	4.1
cephalic	3.4	laughing	2.1
affective	2.7	nystagmus	1.4
visual	2.1	**changes in heart rhythm**	**19.2**
gustatory	0.7	tachycardia > 100	14.4
auditory	0	increase in heart rate < 100	6.8
olfactory	0	Bradycardia > -20%	0.7
tonic	**71.2**	Asystolia > 3sec	0.7
unilateral	58.9	extrasystolia	0.0
bilateral	12.3	**autonomic response**	**34.9**
clonic	**58.2**	hypersalivation	17.1
unilateral	46.6	flush	6.2
bilateral	24.7	paleness	0.7
myoclonic	**39.7**	vomiting	0.7
unilateral	24.0	piloarrection	0.0
bilateral	27.4	hyperhidrosis	0.0
version	**44.5**	ictal speech	7.5
head	32.2	ictal aphasia	1.4
eye	30.1	ictal dysarthria	1.4
trunk	11.0	enuresis	2.7
sign of four	11.0	enkopresis	0
last clonus unilateral	14.4	impaired language comprehension	60.3
last clonus bilateral	11.6	impaired reactivity (nonverbal stimuli)	40.4
staring	29.5	language comprehension preserved	37.7
automatisms	**35.6**	preserved reactivity (nonverbal stimuli)	22.6
oral automatisms	21.9	postictal nose rubbing	15.1
manual automatisms unilateral	23.3	postictal coughing	6.2
manual automatisms bilateral	12.3	postictal Todd's paresis	4.1
dystonic	**16.4**	postictal agitation	8.2
unilateral	13.7	Postictal aphasia	8.2
bilateral	4.8	postictal amnesia	19.2
vocalisation	42.5	Postictal dysarthria	1.4
restlessness	28.8	postictal anomia	0.7
arrest	23.3	postictal alexia	0.7
hypokinetic	2.7	postictal psychic alteration	0.7

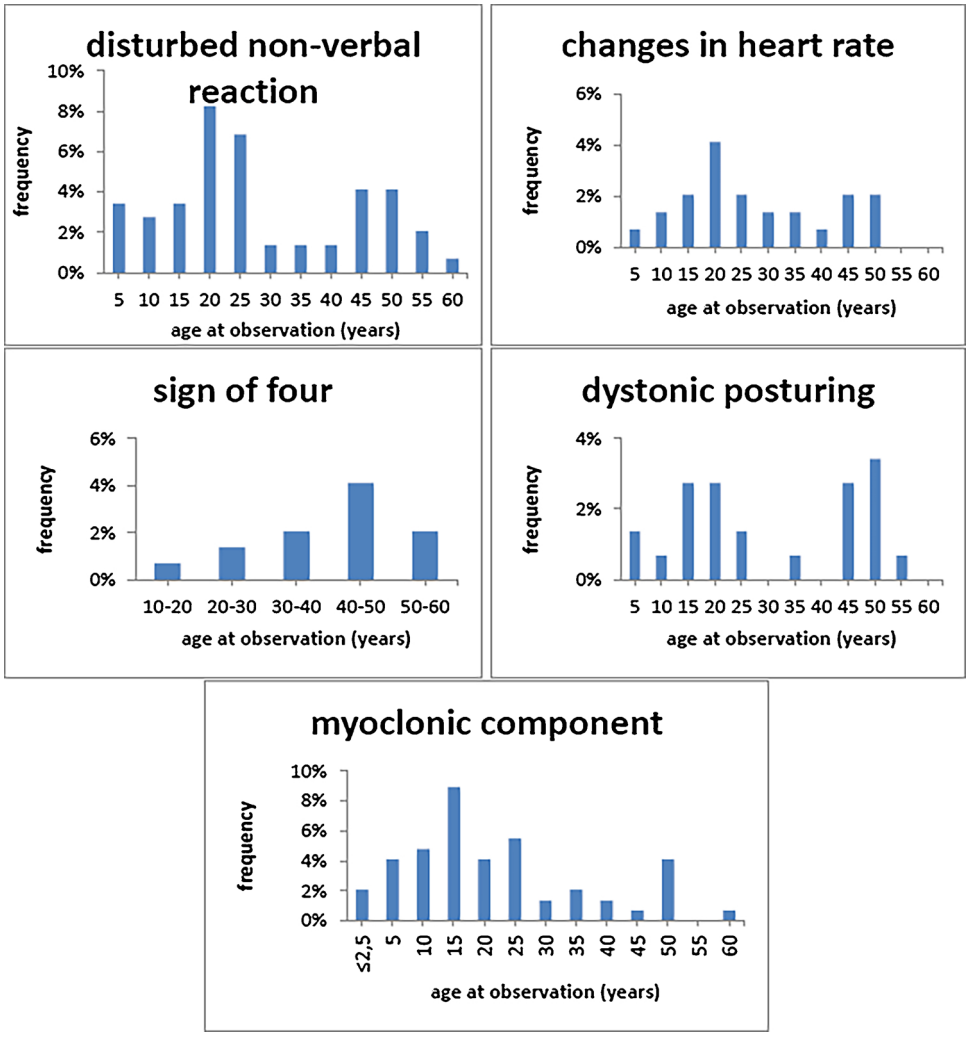

Fig. 1. Visualization of patient numbers with a given semiological sign in relation to age groups. Logistic regression with age as independent variable showed disturbed non-verbal reaction ($p = 0.009$), changes in heart rate ($p = 0.014$), sign of four ($p = 0.019$) and dystonic posturing ($p = 0.026$), and as significantly more observed with increasing age. Myoclonic components were significantly more common in younger patients ($p = 0.037$).

only in patients 13 years and older. Three out of five patients age three years or younger had bilateral spasms.

3.3. Longitudinal descriptive case study

Nineteen patients underwent repeated monitoring at two or three different points of age with an interval of more than one year. A longitudinal descriptive case study of one patient with three different monitorings at age two, seven and ten years is displayed in Table 3 exemplifying the intraindividual evolution of semiological elements over time. Most common semiological feature of seizures over the whole time period was tonic posturing changing from bilateral during the first monitoring to unilateral during monitoring two and three. Semiology evolved from grimacing, automotor and/or hypermotor behavior and autonomic signs at age two to automotor and/or hyperkinetic behavior, eye deviation, postictal nose rubbing ipsilateral and coughing at age seven. With increasing age, lateralizing tonic contralateral posturing occurred, whereas impaired responsiveness was a constant, age-independent feature.

Table 3
Longitudinal case study displaying evolution in semiology sequence during aging of a patient monitored at three different time points (x = semiological feature present; – = not present).

semiology	2 years	7 years	10 years
automotor/hypermotor	x	–	–
tonic posturing	bilateral	contralateral	contralateral
grimacing	x	–	–
version	–	contralateral	–
nose rubbing	–	ipsilateral	–

Ictal and interictal EEG suggested a seizure onset zone right frontocentral. MRI findings indicated a large focal dysplasia and pachygyria in the right frontal lobe matching the EEG findings. The patient underwent epileptic surgery twice. After incomplete lesionectomy and seizure relapse the patient received an anatomic lobectomy of the right frontal lobe due to the extensive focal dysplasia resulting histological of Palmini type IIb. Despite complete resection of the lesion and its surrounds, this patient had only 75% seizure reduction nine years after surgery.

4. Discussion

In the past, FLE has received interest as to how the anatomic organization relates to specific clinical features. Currently, there is a lack of agreement as to how well seizure origin can be localized based on semiology. As opposed to temporal lobe epilepsy, seizures with frontal epileptogenesis pose problems to a specific interpretation in terms of

the epileptogenic region due to diverse and complex behavioral manifestations. FLE shows no gender-specific affection, can manifest at any age, and frequently has sleep-related seizures and clustering (Bagla and Skidmore, 2011). The clinical manifestation of frontal lobe seizures can be classified into perirolandic, supplementauraary, sensorimotor area, dorsolateral, orbitofrontal, anterior frontopolar, opercular and cingulate types with different ictal behaviors (Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy, 1989). None of the semiological elements is pathognomic for one frontal region, however, due to rapid spread of ictal discharges in frontal lobe seizures (Bagla and Skidmore, 2011). Bonini et al. provided a semiological categorization of frontal lobe seizures in correlation with anatomic organization dividing into four main groups: group one – elementary motor signs and involvement of precentral and premotor regions, group two – combination of elementary motor signs, non-integrated gestural motor behavior and involvement of both premotor and prefrontal regions, group three – integrated gestural motor behavior with distal stereotypies and involvement of anterior lateral and medial prefrontal regions, group four – seizures with fearful behavior and involvement of the paralimbic system (Bonini et al., 2014). We found no significant age-dependency regarding these subgroups.

Divergent data have been published on the question as to whether there are any typical auras in frontal lobe epilepsy, ranging from no aura at all to unspecific auras in the majority of patients. The symptomatology of auras is assumed to reflects location and extent of the symptomatogenic zone particularly well and may provide localizing and lateralizing information (Foldvary-Schaefer and Unnwongse, 2011; Ye et al., 2012). Unilateral somatosensory auras have not only been reported with parietal, central or insular but also with frontomesial origin (Beleza and Pinho, 2011). Additionally, authors (Beleza and Pinho, 2011; Foldvary-Schaefer and Unnwongse, 2011; Jobst et al., 2000) describe aura subtypes with cephalic, epigastric, olfactory, autonomic and psychic components in patients with frontal lobe epilepsy. Fogarasi et al. reported auras in only three of 14 patients under age seven, two unspecific and one somatosensory aura (Fogarasi et al., 2001). Our study group confirms these findings as an aura was reported by 20.5% of the patients. Most common auras were somatosensory (11%) and epigastric (4.8%) but covered also other subtypes as described above. Patients under six years never reported an aura, which may be partly due to a reporting and observation bias due to limitations at this age to verbalize bodily sensations.

Clinical features of frontal lobe seizures in childhood have been reported to frequently consist of an explosive onset, screaming, agitation, stiffening, kicking or bicycling of the legs, and incontinence (Sinclair et al., 2004). So far, this has not been compared between different age groups, however. We found tonic posturing, impaired language comprehension and myoclonic components as most frequent manifestations in children aged 12 years and younger. In comparison, age-dependent analysis in temporal lobe epilepsy found ictal automatisms (especially complex automatisms), secondary generalization and number of different lateralizing signs more often in older patients whereas the ratio of motor seizure components decreased by age. Independent of age was the occurrence of auras, emotional and autonomic symptoms (Fogarasi et al., 2002, 2007). Stability of semiological manifestation was reported in children from age 6 on, whereas in infancy semiological features suggesting spread to frontal lobe were reported with symmetric motor phenomena and posturing of the limbs as well as head nodding like in infantile spasms (Brockhaus and Elger, 1995).

To our knowledge there is only few data on age-dependency of semiology in FLE. Some studies discuss variance between children and adults regarding seizure semiology, mostly analyzing certain subgroups without covering the whole age spectrum in their study group (Fogarasi et al., 2005, 2001). Battaglia et al. analyzed 18 children under 12 years with lesional FLE. Typical patterns were represented by complex motor, especially hypermotor seizures. They were also found in combination with tonic, gelastic, automotor and versive seizure elements. Semiological sequence was often stereotyped for a given patient. Even though bilateral tonic-clonic seizures were confirmed as rare and epileptic spasm were rather frequent, other aspects of semiology, especially versive seizures and complex motor seizures, did not differ greatly from those in adult series (Battaglia et al., 2007).

Another study in 14 children below age seven discussed possible age-related differences in motor signs between children and adults. Even though all children had motor seizures with tonic seizures or clonic features, hypermotor components and complex motor automatism were not observed whereas epileptic spasms and behavioral changes were frequent. In contrary to adult series they did not document any versive or bilateral tonic-clonic seizures (Fogarasi et al., 2001).

In contrast, our studied population is about ten times as large and includes a much wider age range of patients. In contrast to earlier studies, clonic features and hypermotor components did not show significant age-dependent changes in the age range from 0 to 70 years. Due to limitations in interactions during the first years of life, signs as aura-like sensations may be underestimated and verbal responsiveness is less reliably assessable in this age group. In our cohort, the subgroup of patients below two years was under-represented (two patients), precluding a separate assessment which would be particularly interesting due to the rapid alterations myelination which may alter propagation in this very young age group (Deoni et al., 2015).

Hamer et al. reported seizure semiology in less than three year-olds without further discriminating between epilepsy syndromes. Overall, motor seizures were the most frequent seizure type dividing into epileptic spasms, tonic, clonic, and hypomotor seizures, findings that were are also discussed in Yu et al. and correspond very well to our findings which found epileptic spasms and myoclonic components as typical in the youngest (Hamer et al., 1999; Yu et al., 2013), suggesting an age-dependent manifestation independent of the exact seizure origin. Dulac et al. linked diffuse cortical hyperexcitability of the immature cortex and fast diffusion of paroxysmal epileptic activity with the manifestation of epileptic spasms (Dulac et al., 1994). Similar mechanisms may account for the frequent myoclonic components in this age group.

There is evidence from various imaging methods that myelination and cortical organization undergoes considerable changes during brain development until age three to four and during adolescence (Chugani et al., 1987; Deoni et al., 2015; Moon et al., 2011; Qiu et al., 2010; Sherman et al., 2014). This long ongoing process contributes to the development of for cognitive and motor functions (Friederici et al., 2011; Schmithorst et al., 2002). Diffusion tensor imaging data retrieved from different age groups has shown that white matter maturation entails increasing values of fractional anisotropy as well as decreasing values of apparent diffusion coefficient. A recent study described changes in brain microstructure during infancy and childhood as an exponential function between apparent diffusion coefficient (ADC) values and age. These values decreased in all brain regions with increasing age (Bültmann et al., 2017).

This study has several limitations due to its retrospective nature, patient numbers and the specific setting of observations. Patient numbers are not evenly distributed over the age classes investigated. Seizure semiology and evolution may also have been influenced by tapering of medication during video-monitoring, which affects propagation of ictal discharges and seizure severity. Another methodological limitation of the study is classification of frontal lobe epilepsy based on video-EEG and imaging which may not always be able to exclude extra-frontal onset particularly in pediatric cases.

5. Conclusion

This cross-sectional study shows age-dependent changes of semiological features in frontal lobe epilepsy. In particular, simple

lateralized motor signs like unilateral dystonic posturing, sign of four and version were uncommon in very young patients, as well as unilateral manual automatisms, vocalization and postictal aphasia. In contrast, bilateral spasms occurred at youngest age, and myoclonic components where witnessed less often with increasing age. Whereas limitations in interaction may bias the validity of the assessment of auras and verbal reactivity, alterations in motor phenomenology is assumed to represent maturation of connectivity, e.g. the more frequent observation of unilateral signs (sign of four, dystonic posturing, version) during higher age may reflect ripening of interhemispheric inhibition (Ciechanski et al., 2017) and more limited seizure spread within one frontal lobe. Another limitation is caused by the analysis considering mostly common semiologies as features seen less than five times from the patient cohort were censored. Further studies are needed to evaluate these aspects, especially regarding the first 24–36 months of brain maturation.

Disclosure

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