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Research Paper

Ictal Fear in Children: Localizing Value and Insights Into the Mechanisms of Fear in the Developing Brain

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ABSTRACT

Background: Rigorously documented ictal fear is infrequent, and its anatomoclinical correlations remain poorly defined. We aim to determine its localizing value and provide novel evidence of the clinical importance and theoretical meaning about ictal fear and emotional processes in children.
Methods: Of 1624 consecutive pediatric patients assessed, we identify seven with carefully defined and strict video-electroencephalography (EEG)-recorded ictal fear (130 seizures), two with additional intracerebral stereo-EEG and electrical brain stimulation examinations. A comprehensive study of EEG and semiology is performed, comprising synchronized analysis of seizure origin and propagation and supported by neuroimaging.
Results: Despite activation of distinctive anatomically distributed regions in different patients, a common clinical picture emerges. Ictal fear seems more frequent in girls, and a right hemispheric predominance is observed. Additionally, a particular common state of fear was documented, suggesting that such event is embodied by the activation of a specific neural network of elements scattered about different areas.
Conclusions: We describe a common clinical setting for ictal fear in children, clarifying diagnosis, localizing value, and medical/surgical prognosis. We delineate the variable underlying networks implicated in ictal fear, including highly interconnected structures (the insula, hypothalamus, and parietal lobe), integrating our findings into the modern theories of fear.

Introduction

Despite recent advances, the neurobiology of fear in humans is still in its infancy. Various cortical regions together with cerebral and brainstem nuclei are known to participate, but it remains unclear how they all inter-relate, with likely massive reciprocal interactions between all the components. Besides, there are many other structures that are likely to play key roles, but knowledge about them is very limited and mostly comes from animal studies.[1,2]

Epileptic seizure phenomena are closely related to the physiological functions of the involved brain regions or circuits, providing invaluable information as a window to the principles of cerebral organization in relation to even the more complex aspects, including cognition, emotion, and self-identity. In some focal onset epileptic seizures, patients may experience subjective symptoms of being afraid and manifest intense agitation, screaming, and facial expressions of fear, many times posing diagnostic difficulty, especially in children. The precise anatomic origin of such intense ictal

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emotional behavior is not fully understood, and the mechanisms by which the epileptic discharges provoke these phenomena are unknown.[3] Careful analysis of the progression of clinical phenomena and correlation to the neural discharge in terms of frequency, timing, and location, not only at onset but also throughout the seizure, is critical to understand the relationship between clinical semiology and the underlying anatomic networks.[4]

Besides, although much evidence exists for maturation differences in the mechanisms of emotional processing and particularly fear, no strictly documented real-time ictal studies have carefully addressed this in pediatric epilepsy patient series. Studies tend to mix adult and pediatric ages, not manifestly attempting to discern possible particularities related to maturation. Furthermore, in spite of the fact that most of the literature apparently displays higher percentages of onset of ictal fear in childhood age, the majority of reports take place in adulthood. Moreover, most have relied basically on diagnostic interview and chart reviews but not actually video-electroencephalography (EEG)-recorded seizures, often with vague descriptions of fear and mainly oriented only to medial temporal lobe structures.[5]

We herein present a series of exclusively pediatric patients, with carefully defined and strict video-EEG-documented ictal fear, comprising synchronized analysis of seizure origin and propagation and supported by high-definition neuroimaging. Our objectives are to determine its localizing value and to describe clinical scenarios that can help clarify diagnosis as well as the medical and surgical prognosis in these children. We also aim to contribute to the understanding of the anatomic networks implicated in ictal fear, to build new hypotheses, and to provide insights into its physiopathology. Furthermore, we attempt to integrate the findings into modern theories of emotion and fear in particular.

Materials and Methods

Patients were retrieved from video-EEG monitoring unit records, analyzing 1624 consecutive pediatric (<16 years) patients admitted for long-term monitoring at the same level 4 epilepsy center (Hospital Universitario La Paz, Madrid), to include only those with fear as a fundamental seizure manifestation. We initially incorporated only those in which the actual words fear, fright, or panic were part of the patients' description on a video-EEG-recorded seizure or part of the brief explanation motivating the study. Data were documented on specially designed and anonymous data sheets and tables, consistent with hospital research ethics committee guidelines.

We identified 12 patients fulfilling our initial inclusion criteria. Four of these were excluded due to normal video-EEG recordings and a final diagnosis of nonepileptic paroxysmal events (two with confusional/incomplete awakenings, one with psychogenic seizures, and one with benign paroxysmal positional vertigo). The remaining eight patients had epileptic ictal fear, but one was excluded due to inconsistency of the fear phenomenon, leaving a final total of seven patients and 130 recorded seizures. All selected patients had two or more video-EEG-recorded epileptic seizures consisting of early-onset (within the first five to 10 seconds of the seizure) stereotyped fear as the main ictal phenomenon and documented preserved consciousness throughout all or most of the episode. All had 3T magnetic resonance imaging and, many of them, also a positron emission tomography.

Detailed ictal clinical semiology features were acquired from the immediate description obtained from the patients, from direct examination by either an epileptologist or a specialized nurse/EEG technician, during and around the actually recorded seizures and from later inspection of the video recording. Careful attention was paid to clarify that manifestations were a stereotyped ictal fear phenomenon in itself and not related to other confounding feelings such as fear of having a seizure, feeling of imminent danger, fear of doing something inappropriate while in an altered state, or shame of what other people may think.

Full long-term video-EEG recordings were performed. For each patient, 25 electrodes were placed on the scalp, 19 according to the international 10-20 system for electrode placement and six basal-temporal electrodes according to the 10-10 system. Two patients underwent additional intracerebral (stereo-EEG) recordings for a clear delineation of the epileptogenic zone, including 92-100 contacts. Electrical intracerebral stimulations were performed for anatomofunctional mapping, as well as for seizure triggering and seizure semiology anatomic correlations. Any subjective descriptions or behavior related to fear, as well as other accompanying phenomenology, were correlated with ictal electrical modifications (EEG or stereo-EEG, synchronized electrocardiogram) to corroborate the timing and topography throughout the seizure.

For the cases in which epilepsy surgery was performed, operative and outcome details were noted.

Results

The prevalence of ictal fear in our pediatric population is 0.43%.

Our study reveals common history features. These features include absence of family history of epilepsy or psychiatric disorders and no perinatal complications. All had normal psychomotor development and adequate school performance at diagnosis, with normal neuroexamination. A female gender predominance was recognized (female:male ratio is 5:2). Mean age at onset of ictal fear seizures is 4.32 years (1.50-9.92 years) with six of seven beginning at or before age six years, but the actual mean age at video-EEG documentation is 10.86 years (5-15 years).

Most importantly, a collective fear phenomenology emerges in children with ictal fear, including both subjective and objective manifestations. Hallucinations with persecution scene or complex frightful perceptive illusions occur in most of our patients, and a relatively stereotyped fear behavior arises (including fright facial expression, suppression of ongoing behaviors, leg and arm agitation-beating or shivering, alarm calls/calling mummy, distress vocalizations-screaming). The fear symptom was generally referred to by the children as a detailed and relatively prolonged experience similar to or usually even more vivid than their recall of own past experiences. Overall, fear manifestations remained stable/stereotyped not only for the recorded seizures but also throughout the lifetime history of seizures in each patient.

Seizure durations were between two seconds and three minutes, with fear always appearing within the first few seconds and representing a relatively sustained phenomenology. At least one clear subjective or objective manifestation of the fear state was confirmed to occur within the first five seconds after the initial electrical or clinical ictal changes, whichever happened first. Seizure timing is variable between patients; three patients had seizures mostly during wakefulness, but the remaining four had preference during sleep or on awakening, with no clear time predominance.

Common electrical findings also become evident. Normal sleep and wakefulness background activity and nonreadily visible/low persistence of interictal activity on scalp EEG was the rule. Absent or very subtle/diffuse initial ictal EEG changes, evolving into rhythmic slow patterns, was the typical finding in most. Postictal EEG changes were mainly absent or very subtle. Ictal tachycardia (measurable when seizure duration greater than five seconds) was always present; this was defined as at least a 25% increase in heart rate within the first 30 seconds from onset with respect to individual basal heart rate at rest during wakefulness. It must be

considered that manifestations in these seizures were particularly intense emotionally, sometimes generated violent behaviors, and often arose from sleep/arousal; all are factors that can trigger significant reactive changes in the heart rate. It seems therefore impossible to strictly attribute this tachycardia to the propagation of epileptic discharges involving particular areas of the cortex.

With regard to stereo-EEG studies, for Patient 1 (Fig 1), the fear state was readily correlated with ictal activation and electrical stimulation of contacts located at the right inferior frontal gyrus/frontal operculum and dorsal insular cortices. These same contacts also evoked a clear feeling of seizure onset, ear plugging, and thoracic pressure sensation. For Patient 5 (Fig 2), the fear state was correlated with ictal activation/electrical stimulation of contacts in the ventral insula alone or as additional combined activation of the amygdala and hippocampus. Stimulation of other relevant contacts within the suspected epileptogenic zone, at the middle temporal gyrus, did not evoke fear phenomenology but instead only déjà vécu, which was also part of the overall seizure phenomenology in this patient.

Structural etiology was suspected in all patients, and all showed relevant lesions on magnetic resonance imaging. Two children (Patients 2 and 7) had hypothalamic hamartoma. Another two had focal cortical dysplasia (one was confirmed by pathology, in the right inferior frontal gyrus and dorsal anterior insula, Patient 1, Fig 3; the other was suggested by neuroimaging, in the right medial posterior parietal region, Patient 4). Two other patients (Patients 3 and 5) showed right temporal arachnoid cyst, the latter with additional signs of ipsilateral medial temporal sclerosis. The remaining patient (Patient 6) had bilateral hippocampal atrophy and gliosis associated with diffuse leukoencephalopathy. Etiology could not be further clarified or confirmed in these patients. There is an apparent overall right hemispheric predominance but a variable location of epileptogenic zone/structural correlations, which in most cases seems to involve more than one region/lobe in different combinations. The anatomic correlations that emerge, with high or very high confidence in the epileptogenic zone, depending on available data, confirm the involvement not only of frontal, temporal, and other limbic structures in fear but also of others such as the hypothalamus, insular, and parietal cortices.

All patients had medically refractory epilepsy and almost daily or many-daily seizures. Follow-up periods after the first video-EEG-recorded seizures ranged from five to eight years. After varied

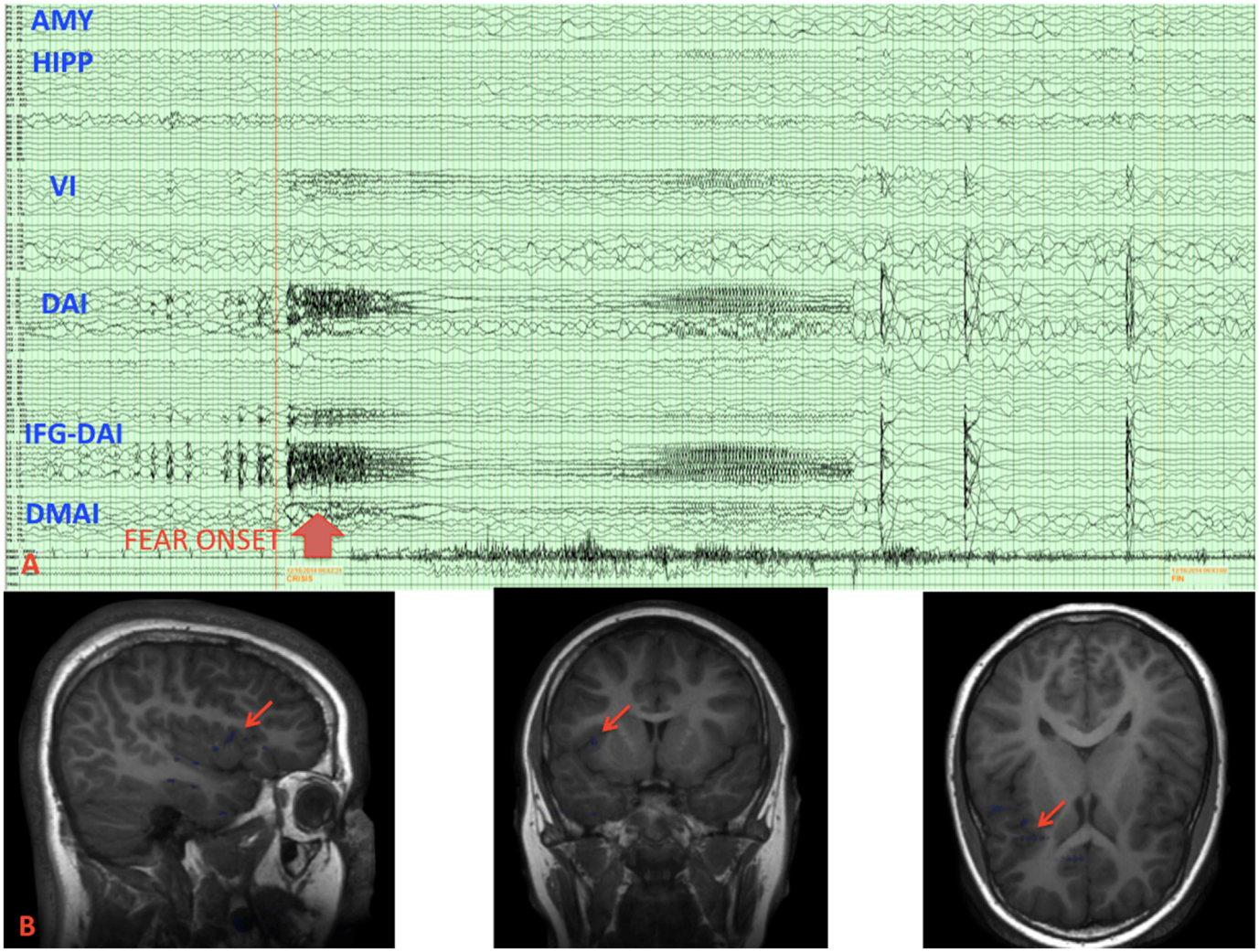

FIGURE 1. Patient 1: (A) ictal stereo-electroencephalography. AMY, amygdala; HIPP, hippocampus; VI, ventral insula; DAI, dorsal anterior insula; DMAI, dorsal mid-anterior insula; IFG, inferior frontal gyrus/frontal operculum. (B) Hybrid neuronavigation image depicting position of some electrodes, highlighting dorsal anterior insular contacts (red arrows) involved in fear semiology (transfrontal insular electrode). The color version of this figure is available in the online edition.

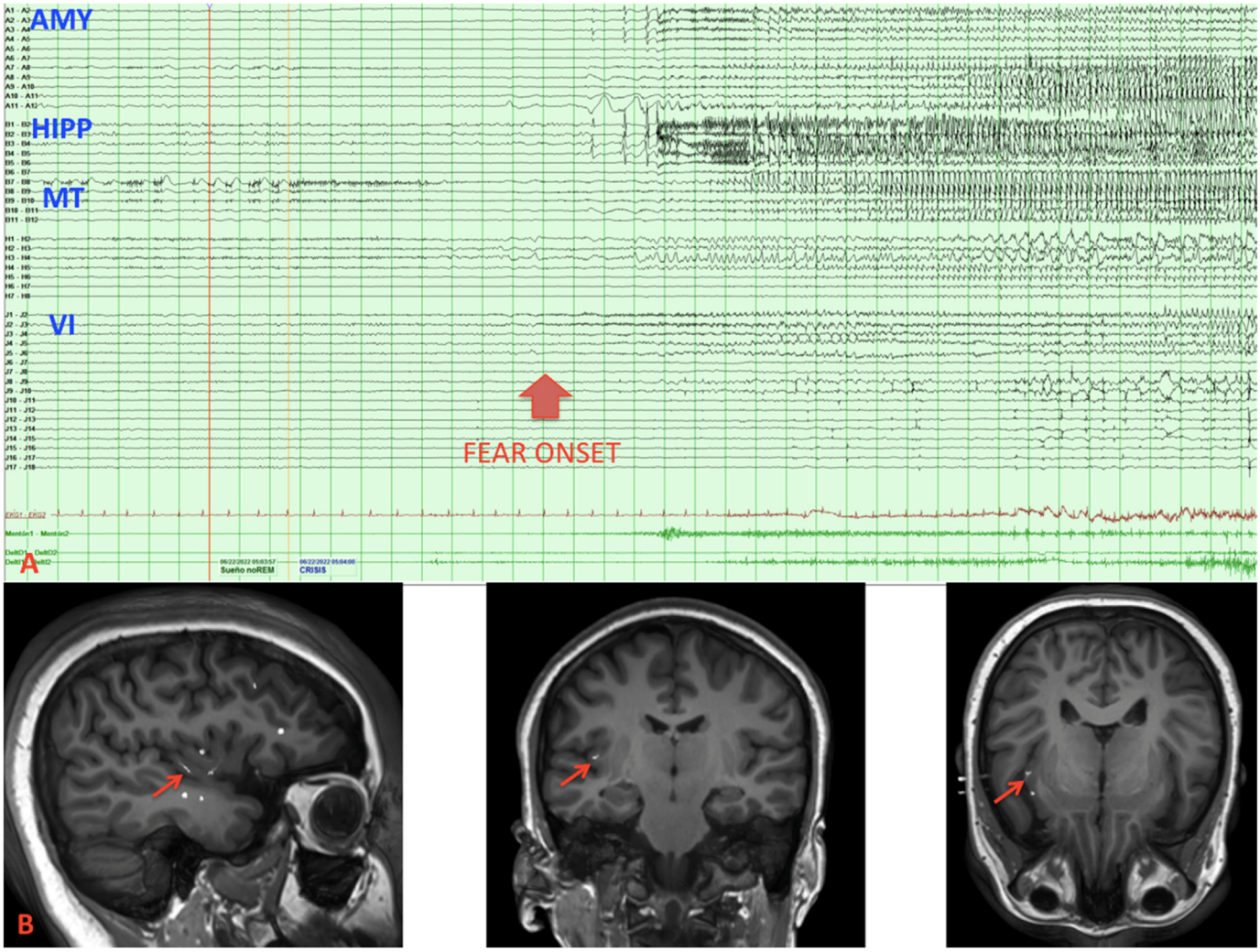

FIGURE 2. Patient 5: (A) ictal stereo-electroencephalography. AMY, amygdala; HIPP, hippocampus; VI, ventral insula; MT, middle temporal gyrus. (B) Hybrid neuronavigation image depicting position of some electrodes, highlighting ventral insular contacts (red arrows) involved in fear semiology (transparietal insular electrode). The color version of this figure is available in the online edition.

medical and surgical interventions, the only two seizure-free patients at the latest follow-up were the ones in whom complete surgical resection was feasible.

Further details of findings for each patient are summarized in Table.

Discussion

Although this is the largest series of its kind, the limited final number of patients included could evidently constrain some of the assumptions that are made. In most aspects, a clear tendency is observed that correlates with the medical literature, whereas other novel findings offer new perspectives in the understanding of ictal fear and fear itself.

Precise documentation of ictal fear in children is rare (<0.5%). It is evident, however, that our series does not necessarily represent the global picture of ictal fear in children, as many may not undergo video-EEG monitoring or simply not present seizures concomitantly. However, it may help set a standard for a more precise analysis of this feature. We did not find any stated percentages for ictal fear in children in the literature, and we observed heterogeneity across studies. Of course, documenting fear as an epileptic phenomenon in the young is not an easy task and many misdiagnose these events as psychiatric or purely sleep derived. Some studies found negative affective auras of different kinds in 15% of subjects in a population of adult patients with temporal lobe epilepsy, with 11% having fear expression.[6] Although some studies speak of ≈7%-10.5% of ictal fear among patients with epilepsy overall at specialized epilepsy centers, populations and defining criteria differ, sometimes being certainly vague or relying on structured questionnaires, with no age distinction made. In one such study,[5] 6.8% of patients reported ictal fear in childhood, but many were adult patients reporting through clinical charts. In a rare exclusively pediatric study involving only patients aged ≥12 years who had undergone epilepsy surgery with video-EEG-recorded seizures, fear expression was found in 15% but other population details were not specified.[7]

A common regular clinical setting for pediatric ictal fear can be yielded from our series. Age at onset is early, and it occurs in otherwise neurologically normal children, with female predominance. Seizure timing is variable, most occurring during sleep or on awakening but many times only depicted in the awake setting. Overall, according to the literature and largely taken from adult or mixed age studies, onset of ictal fear seems more frequent in

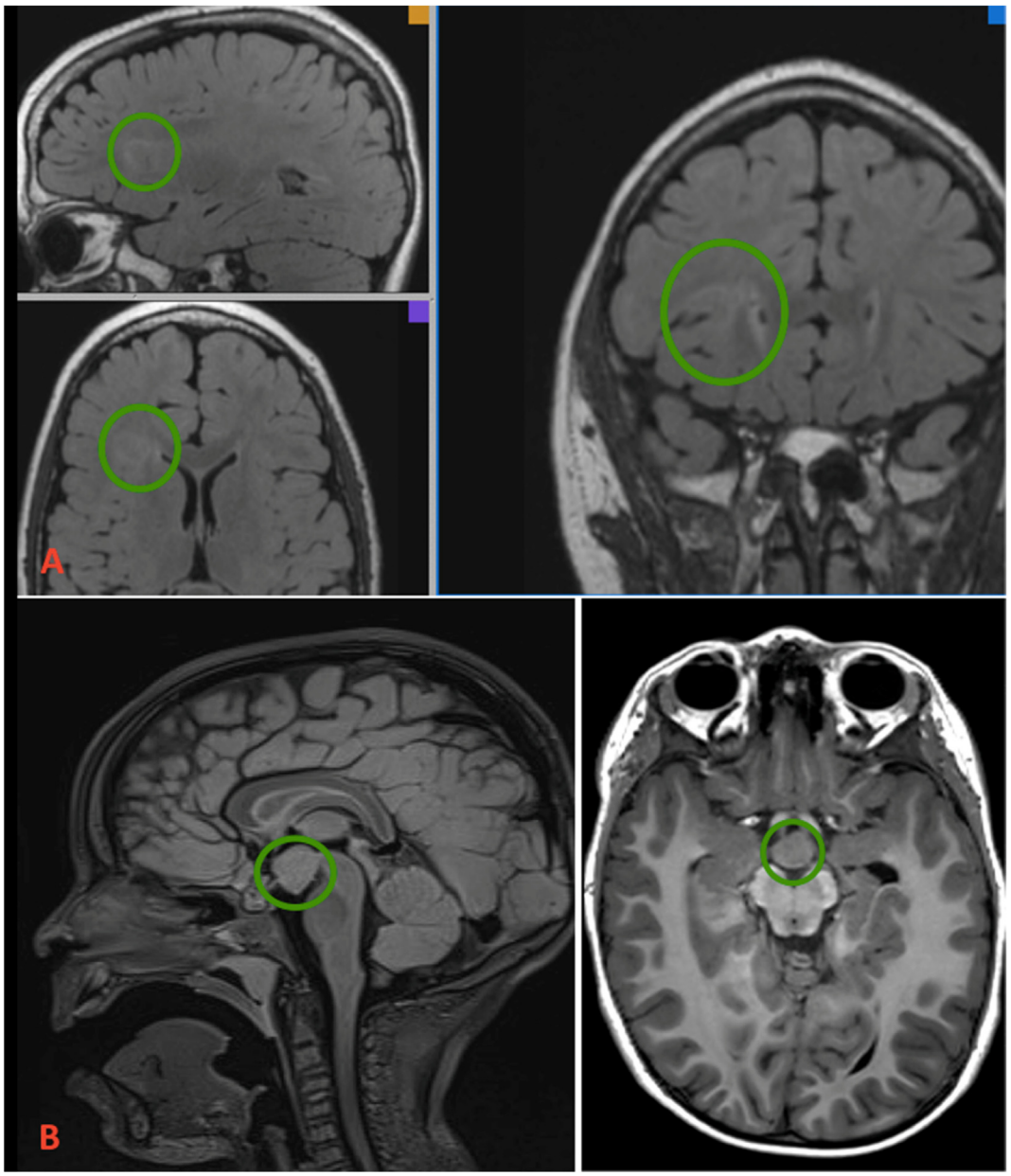

FIGURE 3. Magnetic resonance images showing epileptogenic lesion (green circles) for Patient 1 (A)—focal cortical dysplasia at the right frontal and dorsal anterior insula—and for Patient 2 (B)—hypothalamic hamartoma at tuber cinereum. The color version of this figure is available in the online edition.

childhood.[2] One study seemed to correlate fear expression with younger age, but all patients in the study were aged >16 years.[8] Early age at onset was described in one of the very few exclusively pediatric case series available, with most aged less than six years.[8] In another mixed series that included seven patients with epilepsy onset in childhood (only three were children at the time of study), all but one had onset at less than five years.[9] In relation with gender,[5,6,9,10] female reporting predominance has been shown in some studies, with differences more prominent in adulthood, although some report that more boys than girls appear to have ictal fear in childhood that disappears in adult age. Other studies found no relationship of fear with age or gender when compared with the overall population with focal epilepsy.

A clear picture emerges in our study with regard to ictal fear phenomenology in children: it has a sudden onset and offset, it is nonrelated to real environmental stimuli or even normal thinking, and it is uncontrollable. Objective and conscious subjective fear phenomena occur in association. Hallucinations with persecution scenes or complex frightful perceptive illusions occur in all but one of our patients (perhaps due to the shorter duration of her seizures), and we recommend this should be consistently interviewed for. Fear behavior is a constant, and searching and clinging to a family member in pursuit of close social protection seems almost a hallmark in this setting. Covering the face with both hands was seen in >50% of patients. When detected, these objective features should prompt further inquiry, in search of fear. The available literature has basically dealt with ictal fear either from the more subjective or from the objective point of view. Although conscious sensation of fear has been intensely involved with temporal lobe epilepsy, it has also been noted that behavioral modifications suggestive of intense fear or aggression were related to the frontal lobe, or at least to the involvement of frontotemporal neural networks.[9,11] One interesting

TABLE.
Clinical and Laboratory Data

Patient Data	P1	P2	P3	P4	P5	P6	P7
Gender	Female	Male	Male	Female	Female	Female	Female
Age at fear seizures onset	5 years 4 months	1 year 8 months	1 year 6 months	2 years 10 months	6 years	9 years 11 months	3 years
Relevant previous history (age)	No	No	Enteroviral meningoencephalitis (17 months); R temporal arachnoid cyst resection (3 years)	No	Surgery for L hand and feet polydactyly (7 months)	T-cell acute lymphoblastic leukemia (in remission), bone marrow transplantation, herpesvirus 6 encephalitis (10 years)	Radiosurgery for hypothalamic hamartoma (10 years)
Age at first video-EEG	11 years	5 years	7 years	13 years	15 years	11 years	12 years
Ictal fear seizures							
Frequency	Many daily	Many daily	Almost daily	Many daily	Almost daily	Daily	Many daily
S/W predominance	S, awakening	S, awakening	W	S, awakening	S	W	W
Triggers	Mixed up sounds, scary/creepy situations	No	Mixed up sounds, nervous tension	No	Mixed up sounds	No	No
No. of recorded seizures (scalp EEG/SEEG)	50/32	2	11	2	5/2	12	14
Duration	5-33 s	45-55 s	15-180 s	50-60 s	150-180 s	2-8 s	2-4 s
Detail of fear experience	Preceded by oppressive epigastric sensation. Scenic experience: "unknown man threatens and chases me, I run away."	From surroundings (e. g., a curtain) "it looks like something bad (like a monster), but then I realize it isn't."	Preceded by "burning" feeling over abdomen, chest, and arms. Feeling of fear due to "threat, which is actually happening," "something scary/a ghost threatening and approaching."	Visuoscenic experience: "unknown man chasing, attacking and killing all my family."	Preceded by hearing a mix-up of various loud sounds coming from real environment that "turn into a creepy noise combination." Fear feeling and fear-escape behavior.	Mild-moderate subjective fear "because it seems as if someone might grab me."	Fright sensation referred to abdominal area.
Other associated phenomena	Early ictal pouting. Evolves into ear plugging and word distortion. Sounds become annoying and too loud. Integrated complex motor behavior, hyperkinetic. Ends with R periocular clonic movements.	Covers face with hands.	Covers face with hands or shirt. Sometimes concomitant ear plugging. Sounds become annoying and too loud.	Covers face with hands. Ictal pouting. More or less integrated complex motor behavior, hyperkinetic.	Sometimes dejà vécu, fluorescent white lights, nasal pain-paresthesia, dizziness, laryngeal constriction, dysarthria, nausea-hypersalivation. Most followed by L oculocephalic version, bilateral tonic-clonic.	Covers face with hands. Perceptions: "the world slightly pauses," "I cannot pay attention," "I cannot listen to myself."	Grimacing. Startle response. Isolated asymmetric epileptic spasms.
Other seizure types	No	Gelastic	No	No	No	Epileptic spasms at later stages	Minor tonic seizures in sleep. Epileptic spasms with gelastic component
Scalp interictal EEG epileptiform abnormalities	R frontal	L frontotemporal	R frontotemporal	Midline (Cz-Pz)	R frontotemporal	L frontocentral	L frontal
	S	W, S	W, S	W, S	W, S	S	W, S
Scalp ictal EEG							
Initial changes	None/subtle	None/subtle	None/subtle	None/diffuse/ medial central-parietal	None/subtle	Diffuse delta	Diffuse/L frontal slow/attenuation
Evolution	R frontal rhythmic slow	L frontotemporal rhythmic slow	R frontotemporal rhythmic slow	None/diffuse	R frontotemporal rhythmic slow	Diffuse/L temporal slow	None
3T MRI	R inferior frontal gyrus FCD	Hypothalamic hamartoma	R temporal arachnoid cyst (surgically treated), R medial temporal sclerosis	R medial posterior parietal FCD	Small R temporal arachnoid cyst	Extensive supratentorial leukoencephalopathy, bilateral hippocampal atrophy, and gliosis	Hypothalamic hamartoma
PET	R frontal hypometabolism	L temporal (medial and anterior-lateral) hypometabolism	Bilateral medial temporal hypometabolism		R temporal (pole and superior temporal gyrus) hypometabolism		
SEEG abnormalities (interictal and ictal)	R inferior frontal gyrus/frontal operculum and dorsal anterior insula				R middle temporal gyrus and ventral insula		
EZ hypothesis	R inferior frontal gyrus/frontal operculum + dorsal anterior insula	Hypothalamus + L temporal	R temporoinsular	R medial posterior parietal	R middle temporal gyrus + ventral insula	L temporal + frontocentral	Hypothalamus + L frontal

(*continued on next page*)

TABLE. (*continued*)

Patient Data	P1	P2	P3	P4	P5	P6	P7
Confidence in EZ	Very high	High	Low-moderate	High	Very high	Low-moderate	High
Surgery	R inferior frontal gyrus/frontal operculum and dorsal anterior insula tailored resection	Ventriculoscopic disconnection of hypothalamic hamartoma	No (parents rejected SEEG and surgery)	No (patient rejects surgery arguing psychological reasons)	SEEG-guided radiofrequency thermocoagulation.* Subsequent R anterior temporal lobectomy and extended resection including R ventral insula†	Vagus nerve stimulator	No
Follow-up (since ictal fear recorded seizures)	5 years	5 years	8 years	8 years	6 years	5 years	8 years
Outcome	Seizure-free (2.5 years after surgery)	>75% seizure reduction in 9 first months, now daily but much briefer seizures (<4 s), 5 years after surgery	No improvement	No improvement	*Seizure-free for 3 months, then only subjective phenomena for 9 months. †Seizure-free for 5 months	No improvement	No improvement

Abbreviations:
Cz = Central midline electrode
EEG = Electroencephalography
EZ = Epileptogenic zone
FCD = Focal cortical dysplasia
L = Left
MRI = Magnetic resonance imaging
P = Patient
PET = Positron emission tomography
Pz = Parietal midline electrode
R = Right
S = Sleep
SEEG = Stereo-EEG
W = Wakefulness

study analyzed them in combination, but in an adult population with temporal lobe epilepsy[6]; they found negative auras were significantly associated with fear expressions, especially in the younger ages. Our study tries to go further: fear states should perhaps not be thought of as static functional states or just as a fixed sequence of triggering stimuli, conscience of fear, and behavioral manifestations. Fear states are temporally extended and dynamic in nature, and all components may become intermingled. The timing of this process would extend from the cues that initiate it through to the stimuli encountered as it unfolds, the response and individuals' own perception of the interaction between the two, and the reestablishment of homeostatic balance. Although this makes things more complex, it also imposes limits, since specific neural components come into play at specific points in time. It has already been speculated that in intense ictal fear, with coordinated physiological responses, the discharge may involve or interfere with a complex processing network involving orbitoprefrontal, anterior cingulate, and temporal limbic structures,[9] as well as perhaps the insula and other relevant pathways and subcortical nuclei. It therefore becomes more interesting to acknowledge that in our series, ictal fear phenomena seemed to involve neural tissue more extensively, leading to the speculation that fear is in fact a diffuse cerebral function. Strikingly, in all our cases, there was an aura of stimulus (that can still be considered an exteroceptive stimulus, although perhaps pathologic), so fear behavior always appeared connected to a fear-evoking experience. A different series of pediatric patients with ictal fear did in fact note that manifestations were often accompanied by complex visual hallucinations and psychosis-like complaints.[8] Other series with detailed subjective citations have shown some patients clearly describe fearing violent hallucinations.[9] It is worth emphasizing that merely thinking about stimuli, which are not necessarily occurring, can trigger human fear. Could this perhaps be the reason why we apparently find no triggering stimuli in ictal emotional phenomena? Much in us arises from worrying about what might happen or be, often to the point of distorting what actually is. This aspect of fear induction in humans probably also contributes to the impression we have that fear depends very much on conscious experience.

On other matters, fear behaviors differ in relation to the context in which they occur. A major contextual factor in the integration of a fear scenario with a concordant behavior is the availability of an escape option or whether the threat seems inescapable, and even perhaps if the threat actually needs real escaping, as is the case of ictal fear. In our study, it was confirmed that, even in home settings, behavior is still stereotyped, and the most reasonable response was always seeking familiar adult individuals.

We found no single localization predominance for ictal fear in children, but a right hemispheric lateralization is apparent. This finding perhaps confirms the involvement of various structures linked to fear. Since the fear state seems to have variable seizure onset origins, it is the other accompanying features that help with localization of the epileptogenic zone. Fear seizures have a variable duration, ranging from only a couple of seconds to up to two to three minutes, but it is consistent for the same individual. Seizure duration seems related to differences in location of discharges. Longer seizures and late loss of awareness were more typical of seizures with major temporal lobe involvement. Auditory-related features, such as ear plugging and auditory verbal information or sound distortions, were observed coinciding with all three patients with right insular involvement (plus ipsilateral frontal involvement in one case plus ipsilateral temporal in another two cases). These same patients also described a striking reflex phenomenon related to triggering of seizures by mixed unpleasant noises. Four patients reported abdominal auras, with no clear anatomic correlation. Hyperkinetic motor behavior was seen in two children, one with right frontoinsular involvement and the other with right parietal involvement, but in none with temporal involvement. Ictal pouting, usually related with involvement of the anterior prefrontal

and anterior cingulate cortices,[12] was evidenced in these same two patients. Late ipsilateral periocular myoclonia was frequent for Patient 1, having also been previously described in a child with ictal fear and frontal lobe involvement.[9]

Digging into the literature, we observe that many of these fear and other accompanying features have been described on an individual basis in pediatric patients with ictal fear but they have not been reported in the explicitly synthesized manner that we propose here.[8-10]

Most patients in our series share common scalp EEG features. The fact that interictal activity was usually nonreadily visible or rare on scalp EEG is in concordance with focal epilepsies that originate in rather "deep/hidden" localizations, such as the hypothalamus and other medial-limbic structures or the insular cortex. The initial portions of the ictal patterns, coinciding with the intense fear with preserved awareness, were also either indistinguishable or very subtle, usually consisting of diffuse attenuations, later evolving into rhythmic slow patterns. This overall combination of EEG features can clearly make diagnosis more challenging. Evidence coming from patients undergoing stereo-EEG, including our own, suggests that in intense ictal fear, with coordinated behavior and autonomic features, the discharge may involve or interfere with a physiological complex information processing network. The presence of a concomitant desynchronized activity involving a widespread group of structures is in fact concordant with our scalp findings and was confirmed for the two patients undergoing stereo-EEG. In these intracranial recordings, a clearly defined ictal pattern was documented comprising fast activity at triggering structures, and additional more widespread changes could also be seen showing perhaps functional participation but not strict seizure involvement in various other regions. Ictal tachycardia was present in all patients with seizures of greater than five seconds, with time-locked >25% increase in rate with respect to individual basal heart rate. Of course, the motives for such ictal tachycardia remain speculative. Considering the physiology of fear, an initial ictal subjective sensation could activate specific networks relying on previous experiences in the prefrontal cortex, which in turn projects to other limbic areas that activate the autonomic nervous system and endocrine and peptide systems, among others. Heart rate acceleration has been associated with fearful imagery and a self-directed attention focus and dampening of sensory input ("environmental rejection").[13]

Ictal fear may be the result of early diffuse activation of complex neural circuits, and this is supported by evidence. There is no currently acknowledged single brain region or even small set of indispensable and sufficient structures for processing fear. Our current understanding of fear and its circuitry largely derives from animal studies with their obvious limitations. The scientific study of human fear should go hand in hand with modern theories of emotion and conscious experience, as well as the various human disorders related with it, including epilepsy. Since anatomic systems are based on neural connections between structures rather than spatial proximity,[14] it seems logical that the propagation of ictal discharges should occur within existing brain wiring patterns, albeit in a pathophysiologic context. Networks for processing fear most probably consist of specific subpopulations of cells extended across an array of structures. With regard to lateralization, although either hemisphere can generate fear during electrical stimulation, several studies have found right hemisphere predominance for ictal fear, particularly in adults.[5,9,15,16] Cerebral asymmetry supports many (but not all) theoretical proposals, such as right lateralization of emotional processes, negative emotions, and emotions associated with withdrawal (particularly within the prefrontal cortex). Age could most certainly be a contaminating variable because children and juvenile patients could be less lateralized than middle-aged patients. Age-related differences both in terms of lateralization and localization of seizure onset zone have been described in various studies, supporting the hypothesis that although the limbic system is one of the earliest to fully mature, the development of its neural connectivity is, as that of other systems, incomplete until the postadolescence period. In a study in children, negative ictal emotional expressions such as fear did not have localizing or lateralizing value, whereas positive emotional expressions during seizures were more likely right sided and extratemporal, largely differing from adult experiences.[7]

Synthesis of prior results with our current data suggests that both hemispheric lateralization and distinct topology of emotions are different between children and adults. Emotions seem to incorporate a multicomponential set of phenomena that can be unraveled only through meticulous examination of relations between neurophysiological changes and specific emotion constituents. A few studies have reported elicitation of fear by electrical stimulation of the human cerebral cortex either using intraoperative direct cortical stimulation or through intracerebral electrodes.[17] The amygdala has generally been recognized as central to the neuroanatomic network for fear and is in fact perhaps one of the areas that most frequently have been reported to lead to the induction of fear overall, together with other medial temporal lobe structures.[18] Quite interestingly, in the present and other studies,[9] amygdala stimulation alone was insufficient to evoke fear. Less frequently, fear can be evoked from intracranial stimulation of—or seizures originating from—many other areas, including temporal neocortex and orbitoprefrontal and cingulate cortices 9,19-24 and more sporadically implicating other structures such as occipital[25-27] and parietal[28,29] lobes as well as perisylvian-insular regions.[30,31] Our study exemplifies how the initial activation of different anatomically distributed regions in different patients can elicit a similar state of fear, suggesting that such event is embodied by the activation of a specific neural network of elements scattered about different areas, perhaps mainly integrative cortices and limbic structures that encode different aspects of the event.[18] Our series further enhances the literature with pediatric cases of ictal fear from extratemporal origin. Two are extremely rare stereo-EEG-documented pediatric cases with clearly defined ictal fear with dorsal anterior or ventral insular onset. We believe this adds treasured evidence to the participation of the insula in the global processing of fear and its view as a hub for the interoceptive information about the state of our body and mind and self-representation, underlying the content of our conscious experience of fear.[32,33] Another two cases are the only to our knowledge reporting intense ictal fear in patients with hypothalamic hamartoma.

Seizure outcome was generally bad for patients not undergoing epilepsy surgery, with persistent drug-resistant fear seizures. On the other hand, seizures in the majority of patients never progressed to bilateral tonic-clonic. Surgical prognosis seems more related to the underlying etiology and perhaps surgical accessibility. It is in any case crucial to make a correct and early diagnosis of ictal fear to optimize treatment.

Conclusions

Carefully defined ictal fear in children is rarely rigorously documented on video-EEG recordings; it manifests in a similar clinical setting, usually before age six years and with female predominance. Ictal fear regularly associates fearful hallucinations and a distinctive fear behavior with ictal tachycardia. Ictal fear seizures are focal onset seizures, and we have evidenced varied anatomic origins, with right hemispheric preponderance. Such divergence reflects that fear processing incorporates complex system networks and that other structures (such as the hypothalamus, insula, and

parietal lobe) may play an important role in the early emotional network of children, independently of amygdala activation.

We hypothesize that early ictal fear phenomena may be triggered from various disparate interconnected neuronal areas but only after rapidly involving and perturbing the widely distributed fear-processing neural network. In this sense, a common set of manifestations may be elicited from the initial activation of various distinctive areas.

CRediT authorship contribution statement

Arturo Ugalde-Canitrot: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Conceptualization. **Marta García-Fernández:** Writing – review & editing, Visualization, Supervision, Resources, Investigation. **Andrea Gómez-Moroney:** Resources, Investigation. **Javier Saceda:** Resources, Investigation. **Cristina García de Leonardo Mena:** Resources, Investigation. **Diana Monge Martín:** Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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