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Review

Affect-induced reflex seizures (AIRS): A case series based on a systematic literature review☆

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ABSTRACT

Seizures are commonly thought to occur in a spontaneous, unpredictable manner. However, it is well-established that a subset of patients with epilepsy can experience reflex seizures that are consistently elicited by a specific stimulus. While various forms of reflex epilepsy have been documented in the literature, acute affective states have not been commonly described as a potential reflex seizure trigger.

We performed a systematic literature review to determine if acute emotional states can trigger reflex seizures. We included any case in which reflex seizures repeatedly occurred in response to a patient-specific stimulus that was reported as emotionally relevant by the authors. This yielded our case series of ten patients who have been described to have reflex seizures in response to emotional stimuli. We characterized features of these cases including the following: age, gender, developmental and psychiatric history, seizure semiology and duration, emotional triggers, other reflex triggers, relationship between reflex triggers and seizures, investigations, localization, final diagnosis, treatment, and outcome.

Considerable variability was found between cases. A trend toward limbic seizure semiology with psychic aura originating in networks involved in emotional processing was noted, with temporal lobe epilepsy being the most common, although without clear laterality or gender predominance. In addition, the report of a significant life stressor occurring at epilepsy onset in three of ten patients as well as the initial suspicion that reflex epileptic seizures were psychogenic in three cases both emphasize the role of electroencephalography in assessment of such presentations to avoid missing a diagnosis of epilepsy.

Findings from these ten cases suggest that a patient-specific affective stimulus may trigger reflex seizures in a subset of patients, and that this could be underrecognized or mislabeled as nonepileptic. We encourage future studies with larger numbers to further characterize this phenomenon. Insights gained may enhance our understanding of seizure localization and bear potential treatment implications.

1. Introduction

Reflex seizures are seizures that are consistently elicited by a specific afferent sensory stimulus or an activity undertaken by the patient [1]. These triggers can range from simple (flickering light, hot water, or startle) to more complex (visual patterns, abstract reasoning, or reading). Triggering stimuli may be further classified as intrinsic or extrinsic [2,3]. An important distinction exists between triggering factors in specific reflex epilepsies and facilitating factors that lower the seizure threshold in general, such as chronic stress, sleep deprivation, alcohol withdrawal, and other metabolic or infectious causes of provoked seizures [4,5]. Terms previously used synonymously with reflex seizures include sensory-evoked seizures, seizures with specific modes of precipitation, stimulus-sensitive seizures, and triggered seizures. Roughly 5% of patients with epilepsy experience reflex seizures, with significant age variability within this population [3].

In 2014, the International League Against Epilepsy (ILAE) updated the definition of epilepsy to include patients with reflex seizures [6]. In the strictest sense, a reflex epilepsy syndrome is defined by the presence of reflex seizures alone and the absence of spontaneous seizures [7]. However, this definition has been criticized for being too restrictive given that many patients who are reported to have reflex epilepsy also

Abbreviations: ILAE, International League Against Epilepsy; EEG, electroencephalography; CDSR, Cochrane Database of Systematic Reviews; PNES, psychogenic nonepileptic seizures; AIRS, affect-induced reflex seizures; MRI, magnetic resonance imaging; CBT, cognitive behavioral therapy.

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have spontaneous seizures [3]. Consequently, there is considerable debate in the literature as to whether spontaneous seizures and reflex seizures are two extremes of a continuum [2,5,8].

Numerous forms of reflex epilepsy have been documented in the literature. These include idiopathic photosensitive occipital lobe epilepsy, other visual sensitive epilepsies, primary reading epilepsy, startle epilepsy, language-induced epilepsy, cognitive epilepsy (seizures induced by thinking), eating epilepsy, musicogenic epilepsy, orgasm-induced epilepsy, praxis-induced epilepsy, somatosensory, or proprioceptive-triggered epilepsy (including hot water epilepsy) [7,9–19]. Visual stimuli have emerged as the predominant trigger in reflex epilepsy [8]. Research into reflex seizure mechanisms has led to significant advances in understanding ictogenesis, which has had diagnostic and therapeutic benefit [9,20].

Emotional stimuli are not currently classified as known triggers for reflex seizures. However, there is a strong rationale to explore this relationship further given that stress is the most common seizure precipitant reported by patients [21–27]. There is even some preliminary evidence suggesting that emotional stress may trigger the onset of epilepsy in a small proportion of patients with epilepsy [28]. While it is well-known that chronic stress can lower the seizure threshold, less is known about the potential of acute affective states to trigger reflex seizures.

The notion that emotional stimuli can precipitate epileptic attacks is found throughout medical literature. Stevens was among the first to investigate this phenomenon in the late 1950s by showing that emotionally provocative verbal stimuli could elicit epileptiform discharges in a subset of patients with epilepsy [29,30]. In 1976, Feldman and Paul built upon prior work by using audiovisual recordings to trigger negative emotional responses. Using this technique, they reported being able to induce focal seizures with impaired awareness in certain patients with epilepsy [31]. Dedicated case reports linking reflex epilepsy to complex intrinsic stimuli with at least some emotional component appear in the literature as early as 1975 [32]. However, the reports vary considerably in scope and level of detail. To our knowledge, there has been no dedicated paper looking at this body of evidence. We undertook the present systematic review with an aim to (1) characterize the phenomenon of reflex seizures induced by acute affective states and (2) explore potential insights regarding their localization, natural history, diagnosis, and treatment.

2. Methods

We performed an online search of PubMed, EMBASE, PsycINFO, and Cochrane Database of Systematic Reviews (CDSR) in September 2017 (see Fig. 1 for a schematic representation of the search algorithm). There were 14 initial search terms: "reflex epilepsy," "reflex seizure," "seizures with specific modes of precipitation," "sensory evoked seizure," "sensory evoked epilepsy," "triggered seizures," "emotion-induced seizure," "emotion-induced epilepsy," "stress-induced seizure," "stress-induced epilepsy," "anxiety-induced seizure," "anxiety-induced epilepsy," "panic-induced seizure," and "panic-induced epilepsy." These generated a total of 4287 references, which were then imported into the Rayyan systemic reviews web application (https://rayyan.qcri.org/).

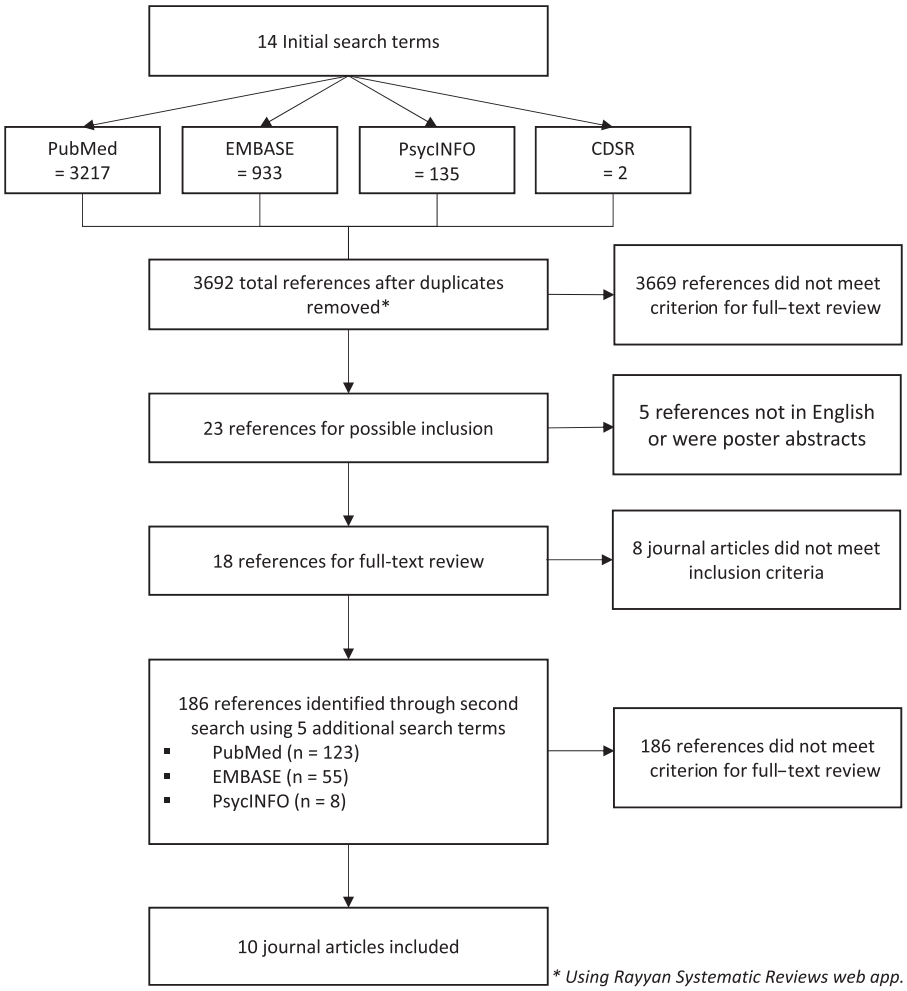

Fig. 1. Using the search strategies outlined in the Methods section, a total of 3878 references were found, with ten of these being selected for inclusion in this review.

Rayyan removed 595 duplicates from the initial search results, leaving 3692 references for initial review.

We excluded 3669 of the 3692 results because there was no relation to either reflex seizures or emotional triggers. The vast majority of the initial search results were obtained using more general search terms such as "reflex epilepsy," which cast a broad net inclusive of other triggers for reflex seizures beyond emotion. Consequently, a large proportion of results were not related to emotion. When we used more specific search terms, far fewer results were obtained. We also excluded articles reporting cases in which the possible relationship between emotion and seizure induction is significantly confounded by other potential triggers including cases of musicogenic epilepsy, praxis-induced reflex epilepsy, orgasm-induced reflex epilepsy, startle epilepsy, and proprioceptive or tactile-related reflex epilepsy (including hot water epilepsy). We also excluded cases of cognitive reflex epilepsy unless the reporting authors explicitly described emotional aspects of the triggering thoughts. Spontaneous seizures were not a criterion for exclusion.

The criterion for full-text review was any case(s) with recurrent reflex seizures occurring in human(s) where the trigger involves an emotional state. Only 23 references met the criterion for full-text review. Five of these references were excluded because they were only available as poster abstracts or were not available in English. Upon full-text review, eight of the remaining 18 articles were excluded for involving reflex stimuli that were primarily related to language [33], diaper change (tactile) [34], cognition [32,35], eating or proprioception [36], crying in infancy [37], singing [38], or pertaining to an isolated event [39]. Ten case reports were included in the final review.

A second search was performed using five additional search terms generated from the initial review: "emotional stimuli-provoked seizure," "provoked seizure," "provoked epilepsy," "cognitive stress-induced seizure," and "reflex experiential seizure." This yielded an additional 186 references whose titles and abstracts were reviewed. However, none of these articles met the previously stated criterion for inclusion.

We classified each case by seizure and epilepsy type(s) based on the most recent ILAE classification system [40,41]. We also documented and/or attempted to postulate seizure localization based on available information for those articles where it was not explicitly provided (see Table 1). Table 1 also contains the following: duration of reflex seizure, any history of visual sensory aura or ictal psychic phenomenon, type of emotional trigger, any brain magnetic resonance imaging (MRI) results, method(s) of epilepsy diagnosis, the suspected etiology, and the authors' term for the type of reflex seizure.

3. Results

We did not identify any case series or reviews exploring this topic. Our search ultimately yielded ten English language case reports published between 1993 and 2017 involving patients with reflex seizures potentially triggered by emotional stimuli (as proposed by the authors). These cases are summarized below, in chronological order of publication, accompanied by details of seizure semiology, phenomenology of triggering emotion, and treatment outcome.

3.1. Case summaries

Case 1. A 51-year-old male presented with a so-called "Pinocchio syndrome" with three recent secondarily generalized seizures that occurred in the context of lying for business reasons [42]. He was found to have a cavernous sinus meningioma that was compressing the medial right temporal lobe. Attacks resolved following treatment with carbamazepine and ablation of the meningioma.

Case 2. A 69-year-old male had a six-year history of focal aware seizures consisting of clonic buccolingual movements and tonic hand flexion following an aura comprising an image of an unrecognized stereotypical face with an expression of "resentment and anger" [43]. Seizures occurred in the aftermath of feeling "frustrated and distressed" in the context of hearing or reading about disasters, political events, or moral issues [43]. These were neither triggered by other negative emotions nor by anger or grief in response to other situations. The triggering emotions were not experienced during or after the aura, and the aura consisted of a distinct visual hallucination as described above. Phenytoin initiation led to two-and-a-half years of seizure control.

Case 3. A 9-year-old male had inv-dup(15) syndrome characterized by early central hypotonia, intellectual disability, autistic behavior, and epilepsy [44]. Since the onset of his epilepsy, he had occasional reflex seizures induced by "emotionally gratifying stimuli" such as cheek-kissing from his mother, or viewing pleasant or funny events. These occurred 5 to 20 s after the relevant stimuli and were characterized by sudden loss of consciousness, upward eye deviation, and rhythmic myoclonic jerks of the axial muscles with electroencephalography (EEG) correlate and no postictal state [44]. Other forms of tactile stimuli to his cheek or the sound of kissing alone did not induce seizures. A number of antiseizure medications were ineffective in controlling both spontaneous and reflex seizures.

Case 4. A 36-year-old, right-hand-dominant, male had intractable focal seizures with impaired awareness from the age of 14 years and did not have any specific triggers in the first several years [45]. Later, he noted that his seizures were consistently and reliably elicited by thinking about or visiting his childhood family home, as well as thinking of his father looking at him. Although he described his childhood as happy, these seizures were heralded by a feeling of fear. He claimed to be able to trigger seizures voluntarily by thinking of his family home and even abort some attacks by diverting his attention away from these thoughts. Although these seizures could be considered to be triggered by specific thoughts rather than affective states, the authors proposed that these thoughts were in fact emotionally significant. Seizures were not triggered by mental stress surrounding other thoughts or memories, recalling other childhood events, or viewing photographs of his father, family, friends, or home. Investigations were consistent with left temporal lobe epilepsy. In addition to treatment with oxcarbazepine, he underwent a left temporal resection. This resulted in roughly two years of seizure freedom.

Case 5. A 20-year-old male had seizures that were reportedly induced by thinking or talking about nursery rhymes and children's games, in addition to the action of sending a kiss with one's hand [46]. The patient achieved seizure freedom with carbamazepine.

Case 6. A 25-year-old, right-hand-dominant, female had a five-year history of partial aware frontal seizures with brief language impairment mimicking stuttering [47]. While some may consider this a specific form of reading or language-induced epilepsy, the seizures were triggered by reading aloud or "stressful" conversation but not silent reading or writing; hence, there was a strong emotional basis. The seizures resolved completely with valproate monotherapy.

Case 7. A 32-year-old female began to have episodes of "dazing out" at the age of six years, shortly after suffering sexual abuse [48]. From ages ten to 23 years, she suffered from generalized tonic–clonic seizures. Following this, she had ongoing impaired awareness events triggered by talking about childhood sexual abuse, her epilepsy, or her father's difficulties with schizophrenia. Her family history was notable for a sister and maternal uncle who had epilepsy. Thirty absence seizures were recorded in the epilepsy monitoring unit, 28 of which occurred while she was providing her history to the authors. This comprised 8% of her total awake time. The reflex events were elicited exclusively by talking about the triggers and not by thinking about them. Her seizures were resistant to trials of phenobarbital, carbamazepine, phenytoin, valproate, and topiramate.

Table 1
Aspects of the ten case reports included in this review are given here for comparison. Seizure and epilepsy types were reclassified as per the recently updated 2017 ILAE Classification system [40,41]. Abbreviations: N/I, not included in case report; Y, yes; N, no; s, seconds; MVA, motor vehicle accident; R, right; L, left.

Case number	Study	Seizure duration	Ictal psychic phenomenon	Reported emotional triggers	Brain MRI	Epilepsy Diagnosis	Seizure localization	Etiology	Author's terminology	Seizure Type(s)	Epilepsy classification
1	Sellal et al., 1993	N/I	Y	lying	R medial temporal lobe compressed by meningioma	interictal EEG	R medial temporal lobe	structural	"partial vegetative seizures"	1) focal emotional and/or sensory seizures; 2) focal to bilateral tonic–clonic seizures	focal right mesiotemporal epilepsy
2	Cohen et al., 1999	10–20 s	Y	frustration, anger, despair	R frontotemporal area 7.5 mm hyperintensity with spoke wheel vascular pattern	interictal EEG	R temporal	unknown	"simple partial seizures"	1) focal sensory seizure progressing to left hemiclonic; 2) focal to bilateral tonic–clonic seizures	focal right temporal lobe epilepsy
3	Aguglia et al., 1999	30–40 s	N	kissing or viewing pleasant events	Normal	ictal EEG	L frontotemporal & R parietotemporal	genetic	"myoclonic absence-like seizures"	1) reflex seizures = myoclonic impaired awareness seizures 2) spontaneous seizures = generalized atonic impaired awareness seizures	combined generalized and focal epilepsy
4	Martinez et al., 2001	60–90 s	Y	thinking of family home or his father looking at him	L temporal lobe indistinct gray-white matter differentiation	ictal EEG	L temporal	structural	"experiential complex partial seizures"	focal impaired awareness cognitive automatism seizures	focal left mesiotemporal lobe epilepsy
5	Bonanni et al., 2004	24 s	Y	childhood games, songs, sounds, action of blowing kiss	Normal	ictal EEG	N/I	unknown	N/I	focal impaired awareness sensory seizures	focal (probable limbic) epilepsy
6	Michel et al., 2004	5–10 s	N	reading aloud or stressful conversation	Normal	ictal EEG	L frontal cortex	N/I	"partial frontal seizure"	focal aware left facial hemiclonic seizures	focal left frontal lobe epilepsy
7	Woods and Gruenthal, 2006	1–7 s	N	talking about traumatic memories	N/I	ictal EEG	Bifrontal	N/I	"absence seizures"	generalized nonmotor (absence) seizures	generalized epilepsy
8	Glass et al., 2006	60–100 s	Y	specific prayer	Normal	ictal EEG	Anterior cingulate (side unknown, but likely R)	unknown	"partial complex seizures"	focal impaired awareness atonic +/− progressing to bilateral clonic seizures	focal right frontal lobe epilepsy
9	Gilboa, 2012	60–90 s	Y	not getting attention from mother	Normal	ictal EEG	L centrotemperoparietal	N/I	"simple partial seizures with secondary generalization"	focal sensory progressing to emotional then asymmetric tonic to bilateral tonic–clonic seizures	focal left centrotemperoparietal epilepsy
10	Tamune et al., 2017	N/I	Y	thinking about MVA	L temporal loss of gray-white matter differentiation and amygdala enlargement	ictal EEG	L mesial temporal lobe	structural	"semiology of seizures was typical of left mesial TLE"	focal impaired aware automatism seizures	focal left mesiotemporal lobe epilepsy

Case 8. A 12-year-old, left-hand-dominant, female had moderate developmental delay of unknown etiology emerging at the age of 2 years [49]. At that time, she developed focal seizures with impaired awareness involving an odd laugh, bilateral arm extension with rhythmic jerking, and occasional left leg extension. She had reflex seizures with every micturition, and reliably with prayer as an emotional response specifically to the phrase "In the name of the Father, the Son, and the Holy Spirit." The latter had occurred since the age of ten years, occurring four to six times daily, and were resistant to trials of phenobarbital, valproate, clonazepam, topiramate, lamotrigine, clobazam, and the ketogenic diet.

Case 9. A 12-year-old female experienced focal aware to bilateral tonic–clonic seizures since the age of five. These began around the time of a parental divorce and occurred in clusters every several weeks [50]. When seizures first began, she reported an initial visual hallucination of trumpets with faces. At the time of assessment, her seizures began with focal sensory aura in her right foot, progressing to tonic posturing of the right leg and both arms, and ultimately to generalized clonic movements [50]. During a prolonged hospital admission, all seizures that occurred during wakefulness appeared in connection to an emotionally-charged situation, particularly when her mother was not paying attention to her or when she was asked to do something she did not wish to do [50]. When her mother was asked to leave, she had periods without any seizures. This may suggest an element of self-induction, although this was not explicitly stated by the authors of this case. She was started on lamotrigine in hospital. On discharge, custody was transferred to her father. She remained seizure-free at four months post discharge.

Case 10. A 50-year-old, right-hand-dominant, female was involved in a motor vehicle accident while driving, three years prior, in which she did not suffer any head injury [51]. However, her mother-in-law was severely injured as a passenger. The patient felt responsible for this and became clinically depressed, requiring treatment with antidepressant medication. One year following the accident, when the event was mentioned, she suddenly became unconscious. A similar event occurred a month later. Since that time, whenever the accident or her mother-in-law's injury was mentioned, she experienced acute onset of confusion with disorientation and various unusual, purposeless behaviors [51]. A diagnosis of psychogenic nonepileptic seizures (PNES) was initially suspected. She was later admitted to the epilepsy monitoring unit, where five seizures were recorded on video-EEG. Two of these were triggered by either talking about the emotional distress experienced secondary to the accident or by reading and writing an emotion-provoking questionnaire. The semiology was typical of left mesial temporal lobe epilepsy, and this was supported by several investigations. Her depression and quality of life improved with the new diagnosis. She was trialed on lamotrigine, levetiracetam, valproic acid, and gabapentin with incomplete response. She was offered epilepsy surgery before deciding to undergo a trial of perampanel, which led to a five-month seizure-free period in follow-up.

3.2. Demographics, natural history, and comorbidity

The age at epilepsy onset for these ten patients ranged from 2 to 63 years with a mean age of 22.7 years. There was an equal number of male (Cases 1–5) and female patients (Cases 6–10). Three of ten had a significant life stressor around the time of epilepsy onset (Cases 7, 9, and 10). Thirty percent of these patients were initially referred for assessment with a suspicion for PNES (Cases 5, 7, and 10). Eight of the ten cases had their seizures captured electrographically (Cases 3–10).

Two cases reported the onset of reflex seizures with the onset of epilepsy (Cases 3 and 10) whereas three of the cases reported several years of delay between the onset of their epilepsy and the subsequent development of reflex seizures (Cases 1, 4, and 7). The remaining five cases did not provide this information.

In terms of seizure risk factors, one patient had perinatal insult without developmental delay (Case 6), and two patients had developmental delay without perinatal insult (Cases 3 and 8). Aside from those who had developmental delay, no others had documented intellectual disability. Only one patient had a reported psychiatric diagnosis (Case 10), which was depression, although psychiatric history was not commented on in eight cases. Only one of ten patients (Case 7) had a reported family history of seizures.

3.3. Seizure and epilepsy characteristics

Of the ten patients, eight had seizures with focal onset. Localizations included left temporal (n = 3), left frontal (n = 1), right temporal (n = 2), right cingulate (n = 1), and in one case, there was no mention of any localization. Four of these eight patients with focal epilepsy had progression to bilateral tonic–clonic seizures. One of the remaining two patients had a genetic generalized epilepsy characterized by predominant absence seizures, while the other had combined generalized and focal epilepsy with bilateral localization consisting of left frontotemporal and right parietotemporal foci.

Half of the patients had a normal brain MRI, whereas 40% of the patients had a lesion visualized. Three cases included an ictal single photon emission computed tomography (SPECT), all of which showed hyperperfusion within limbic structures: two temporal (Cases 4 and 10) and one cingulate (Case 8). One of the patients did not have an MRI reported. Three cases reported a structural etiology, one case a genetic etiology, and the remaining six cases did not report on seizure etiology.

Spontaneous seizures were present, in addition to reflex seizures, in seven cases (Cases 1, 3, 4, 5, 7, 9, and 10). In four of the seven cases, the semiology of spontaneous seizures was the same as the reported reflex seizures (Cases 1, 4, 7, and 10). In one of these (Case 3), the semiology of spontaneous seizures was different from the reflex seizures. The remaining two cases did not clearly mention whether the semiology of the reflex seizures was the same or different from spontaneous seizures.

3.4. Emotional trigger characteristics

Emotional triggers were positive emotions in two cases (Cases 3 and 5), indeterminate emotions in two cases (Case 4 and 8), and negative emotions in six cases (Cases 1, 2, 6, 7, 9, and 10). In the two indeterminate cases, one was thinking about a family home, in a patient who reported a happy childhood and no negative or traumatic events associated with this memory; the other involved an emotional response to a specific prayer. The emotional triggers required an external stimulus in eight cases and could be either internal or external versions of the same stimulus in the remaining two cases (Cases 4 and 5). The specific time from the trigger to the electroclinical event was reported in two cases (Cases 3 and 9), and ranged from 5 to 90 s.

Three cases involved seizures with a specific semiology reported to be exclusively elicited by affect (Cases 2, 3, and 6). Three other cases involved affective states, which were reported to consistently elicit a seizure (Cases 4, 8, and 10). However, information regarding the bidirectional specificity of the relationship between affective trigger and reflex seizures was only present in four of the ten cases (Case 2, 7, 8, and 10). Finally, two cases involved additional reflex epilepsy triggers: reading aloud (Case 6) and micturition (Case 8).

3.5. Treatment response

No discernable trends were noted with regard to effective or ineffective antiseizure drugs in these cases. Five of ten patients became seizure-free, or had significant improvement in seizure frequency,

with medication(s) alone (Cases 2, 5, 6, 9, and 10). Two patients showed an improvement with a combination of medication and surgical intervention for structural causes (Cases 1 and 4). The remaining three cases reported no definite outcomes, though the epilepsy was reported as being refractory to a number of medications (Cases 3, 7, and 8).

4. Discussion

Taken together, these ten cases show that various affective states can induce reflex seizures in some patients with epilepsy. The following terms have been used to describe this phenomenon in the literature thus far: "emotion-induced reflex epilepsy," "emotional stimuli-provoked seizures," and "reflex experiential seizures." Here, we propose the term "affect-induced reflex seizures" (AIRS) to more specifically characterize this entity. We favored the term "affect" rather than the related terms "emotion" and "mood." The term "emotion" refers to a broader construct that encompasses both acute and chronic psychophysiological states characterized by certain subjective qualia. The term "mood," although used differently by different authors, typically denotes a relatively more persistent emotional state such as a period of chronic stress during which seizure threshold tends to be lowered and seizure frequency tends to increase in general. By distinction, the term "affect" can be used to describe a more acute change in emotional state, such as that immediately preceding a reflex seizure. This distinction is reflected in the maxim "affect is to mood as weather is to climate." [52]

In AIRS, an emotional stimulus (that may be intrinsic or extrinsic) triggers a contextually specific affective state that is seen to consistently elicit a seizure within seconds to minutes. The affective state can be positive or negative in valence. Affect-induced reflex seizures may involve intrinsic stimuli similar to cognitive reflex epilepsy. However, only two patients were reported to have seizures in response to purely intrinsic stimuli (thinking about emotional triggers). They both also had events triggered by external presentation of the same stimulus, presumably because this precipitated the causative affective state. Of note, we did not find any report of AIRS in response to intrinsic stimuli alone, suggesting that this is either very rare, underreported, or does not occur.

Prior seizure activity may predispose to the development of AIRS as suggested by our finding that at least three of the patients developed reflex seizures several years after the onset of their epilepsy. In all of the cases, the trigger remained constant and was unique to the individual, again setting this phenomenon apart from the common occurrence of increased seizure frequency in the setting of chronic stress. Furthermore, the specificity of any given patient's affective trigger(s) provides a rationale for the presence of individualized neural connections that are "primed" to respond only to specific emotional stimuli, with abnormal neuronal synchronized firing resulting to reflex seizures. The neural networks involved with normal emotional processing may become hyper-excitable leading to further reflex seizure generation.

An important factor in distinguishing AIRS from the known impact of chronic stress on seizure frequency is the brief time interval between onset of a relatively acute affective state and seizure occurrence. However, we are unable to precisely characterize the duration of this interval at present because only two of the ten cases reported this time (5 to 90 s).

Two of the ten cases demonstrated more than one reflex seizure trigger, including micturition and reading. Given the relative infrequent incidence of reflex seizures overall, this suggests that having reflex seizures in response to a certain trigger may increase vulnerability to having reflex seizures in response to additional triggers. The converse also may hold, in that a single reflex seizure trigger may at different times elicit different seizure semiologies in the same patient. This may be explained by the presence in some patients of disparate trajectories between the afferent and efferent limbs of the ictal reflex loop. Further data are required in order to better characterize the nature of this relationship.

The form of reflex epilepsy described by a given patient may have localizing value. The majority of AIRS cases in this series involve limbic seizure semiology with psychic aura (such as is often seen with cingulate and mesiotemporal ictal evolution). This parallels the finding that seizures induced by visual stimuli are more likely to be occipital in origin [4]. Indeed, several authors conclude that limbic structures are likely active in the AIRS epileptogenic process, as was confirmed by ictal SPECT in three of the patients in this series. However, the situation is likely more complex given that one patient had a clear electroclinical generalized epilepsy syndrome, and another experienced more diffuse (including extralimbic) bihemispheric disease. Neither of these two cases was associated with psychic ictal semiology. The relatively even distribution between left- and right-sided seizure localization among patients with focal epilepsy argues against any specific lateralization associated with AIRS based on information available to date.

Psychogenic nonepileptic seizures and epilepsy often cooccur. Thirty percent of the patients included in this review were initially referred with suspicion for PNES but were subsequently found with a diagnosis of epilepsy in lieu. A similar proportion of patients in this case series had a major life stressor at the time of epilepsy onset. This emphasizes that a history of events triggered by emotion or a major life stressor at time of epilepsy onset should not exclude the possibility of affect-induced epileptic seizures until completion of a thorough diagnostic workup.

There are also a number of potentially similar clinical presentations that would fall within the differential diagnosis of AIRS, as they involve paroxysmal events occurring in the immediate aftermath of acute emotional states. These include (1) primary psychiatric conditions such as PNES, dissociative states, and factitious disorder; (2) affect-induced cardiovascular presentations such as vasovagal syncope and hemorrhagic stroke in the context of emotion-induced hypertension; and (3) other settings, such as cataplexy, migraine with neurologic deficits, and malingering. In the above situations, the distinction from AIRS would not likely be based on any aspects related to the triggering affective state, but rather on differentiating the ensuing paroxysm from an epileptic seizure.

Another differential is the occurrence of an affective state that is actually an ictal phenomenon but may occur so early in the course of a focal aware seizure that it can be mistaken for a seizure trigger rather than part of the seizure itself. The ictal nature of such an affective experience can be established by EEG. However, scalp EEG might not always be able to exclude an ictal basis for an affective experience in so far as not all ictal discharges are detectable on scalp EEG. In the latter case, clinical judgment must be exercised, and a definitive answer might not always be clear.

Given our small sample size and variable findings, and in keeping with available information surrounding other reflex epilepsies, there is insufficient data to propose specific antiseizure medications in this population. However, it is possible that psychopharmacotherapy or psychotherapy, through their influence on emotional processing, may be useful adjuncts for these patients. As with other reflex epilepsies, trigger avoidance may have a role, in concert with other cognitive behavioral therapy (CBT) strategies and biofeedback [53]. Overall, many questions remain to be answered with regard to treatment. This is discussed further along the following conceptual framework.

If we consider that the occurrence of AIRS can involve several successive steps, then we can examine each step to assess its potential candidacy as a target of various therapeutic interventions; AIRS can successively involve (1) exposure to a certain situation, (2) the occurrence of a particular affective state in the context of this situation, and (3) the occurrence of a reflex seizure induced by this affective state. Consequently, an "upstream" level of intervention can involve cognitive behavioral strategies targeting avoidance of situations in which an affect associated with AIRS is likely to arise. Furthermore, this would be particularly applicable to cases involving self-induction of AIRS. However, it is important that a practical balance be sought so that the avoidance does

not result in more disability and quality-of-life impairment than the seizures themselves. Avoidance might not be feasible in every case and can potentially lead to a range of psychopathological consequences through exacerbation of interictal anticipatory anxiety [54]. With regard to the second step in the process, its potential as a target for intervention would relate to the extent to which medications and/or psychotherapy can modify the patient's affective reaction, either quantitatively and/or qualitatively, such that the affective state associated with AIRS is not experienced in reaction to a certain external stimulus. Lastly, with regard to the third step of the conceptualized process above, our current limited knowledge of the pathophysiological mechanisms by which an acute affective state may induce a seizure makes it difficult to offer definite statements on the extent to which it may be amenable to interventions other than antiseizure medications. Ultimately, future research exploring the outcome of various interventions in this population is warranted and could help further inform theories surrounding pathogenesis.

At present, we are unable to comment on any potential association between AIRS and psychiatric disorders, given that only one case report specifically described psychiatric history. Eight of the ten studies made no mention of psychiatric history. This is not necessarily an indication of lack of psychiatric history, especially given that the prevalence of affective disorders in patients with epilepsy is higher than in the general population [55,56]. We suggest that future case reports include psychiatric history, or lack thereof. This would help clarify whether a history of certain types of psychopathology could somehow predispose AIRS, perhaps by influencing excitability of emotional networks. This may parallel observations with other reflex seizure types, such as the report of disproportionate musical tendencies in those with musicogenic epilepsy [18,57].

We also recommend documenting developmental history, age at onset of epilepsy and reflex seizures, the frequency and duration of events, time between the trigger and event, whether the trigger always elicits a seizure (and if not, roughly what proportion of time it does), and whether there are spontaneous seizures as well (and if so, whether these differ in semiology from the reflex seizures). This will allow better synthesis of cases in the future so as to promote further understanding of this topic. To this end, we aim to pursue a subsequent survey study of cases of presumed AIRS across multiple epilepsy centers to provide more accurate prevalence data and to further characterize the gaps in our present understanding of AIRS.

In addition to the data gaps described above, due to the varying scope and level of detail across the case reports, there are other limitations. Given that emotional stimuli have not previously been well-characterized as a reflex seizure trigger, relevant cases may not have been recognized or reported. Also, the definitions and terms used in the literature for reflex epilepsy are inconsistent [5]. Likewise, only one in ten cases (Case 6) met the strictest definition of a reflex epilepsy syndrome wherein there was an accompanying absence of spontaneous seizures, and no underlying etiology was determined. In addition, in half of the cases, although the reporting authors described the emotional aspects of the stimulus, we are not able to exclude the additional or alternative influence of nonaffective cognitive processes. Specifically, the emotions in these cases were associated with lying (Case 1), thinking of one's family home (Case 4), thinking about or hearing nursery rhymes (Case 5), reading aloud (Case 6), and prayer (Case 8). Nonetheless, we chose to include these cases because of the reporting authors' descriptions.

Beyond these cases, various triggers for reflex seizures previously described in the literature have been hypothesized to involve emotion. For example, several studies implicate emotional processing as a central component to musicogenic epilepsy, which localizes to the temporal lobe with a preference for the right side [14,18,58,59]. There are also reports of children with crying-induced or diaper changing-induced seizures [34,37,60]; though, their authors do not propose a primarily emotion-driven mechanism, and it is difficult to be certain regarding the emotional content of these stimuli given these patients' preverbal age. There may also be some emotion-related component to cases involving orgasm-induced seizures, even if not explicitly indicated by the reporting authors [15,16,61]. Distinguishing the emotional component from other well-known reflex triggers remains a challenge for clinicians and patients alike.

Ultimately, a given emotional state occurs in the setting of various sensory and/or cognitive processes, making it difficult to definitively isolate a single seizure-triggering factor. Furthermore, AIRS may itself be a heterogeneous construct; the interplay between trigger and seizure in each case is likely to be unique, in keeping with the individuality of emotional nuance and the uniqueness of the associated epileptic response.

4.1. Conclusion

Patient-specific affective states may trigger reflex seizures in a small portion of patients with epilepsy. We propose the term affect-induced reflex seizures (AIRS) to distinguish this phenomenon from the common occurrence of increased seizure frequency in the setting of chronic stress. In addition, increased recognition of this phenomenon may decrease the risk of misdiagnosis of AIRS as PNES and underscores the role of EEG in assessment of such presentations; AIRS may localize to neural networks involved in emotional processing, including for example mesiotemporal regions and cingulate cortex, although the consistency of this association requires better characterization. We encourage future studies with larger numbers of well-described cases toward greater understanding of this phenomenon, its localization, and potential treatment implications.

Declarations of interest

None.

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