

Genetic reflex epilepsies

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Abstract

Reflex epilepsies (RE) are rare epileptic syndromes with seizures induced by specific triggering factors (either by visual, auditory, somato-sensitive or somato-motor stimulation, or by higher cortical function activities). Their frequency depends on the type of epilepsies, and can reach 25% for photosensitive epilepsy. Spontaneous seizures may also occur. "Reflex seizures" can be classified into a simple "pure" reflex epilepsy and a complex group. The former comprises seizure triggered by simple sensory stimuli or by movements (photosensitive epilepsies). The latter are triggered by complex mental and emotional processes (verbal and non-verbal epilepsies). RE may also be classified into epilepsies that are primary or idiopathic (a genetic basis is likely) and epilepsies that are secondary or symptomatic (with an acquired basis). Reflex epilepsies are generally considered as idiopathic. Primary RE frequently have a family history, an age of onset in early life, a benign prognosis and good response to medication (sodium valproate (Dépakine®), lamictal (Lamotrigine®)), and an electroencephalogram (EEG) with a variable presentation but an almost invariable normality of background activity. Electroencephalographic seizures expression may be partial or generalized. Secondary RE occur later, frequently in patients with an associated neurologic and non epileptic impairment. There is sometimes less stereotypy in clinical expression, a poorer response to drugs for focal seizures triggered by specific stimuli (carbamazepine (Tégrétol®), phenytoin (Dihydantol®)), and frequently an abnormal interictal EEG background.

Key words

Reflex seizures, stimulus-sensitive epilepsy, photosensitive epilepsy, television epilepsy, video-game epilepsy, reading epilepsy, eating epilepsy, startle epilepsy, hot-water epilepsy, musicogenic epilepsy, thinking epilepsy, psychogenic epilepsy.

Photosensitive epilepsy

Disease name and synonyms

- Photosensitive epilepsy
- Television-induced epilepsy
- Video-game induced epilepsy

Definition

Photosensitive epilepsy, the most common reflex seizure, is induced by flickering light, artificial lighting such as malfunctioning fluorescent

tubes, sunlight or by flickering light from behind trees seen from a moving vehicle or reflected from a moving aqueous surface. Pattern-sensitive epilepsy, a less commonly documented syndrome, is usually triggered by patterns such as those formed by escalators, window blinds, and patterns displayed on television (Fylan *et al*, 1997) and video-games (Gastaut *et al*, 1966; Kasteleijn-Nolst Trenité, 1998).

Visually-induced seizures are frequently seen as one feature of idiopathic generalized epilepsies

or as the only type of seizures in “pure” photosensitive epilepsy. With findings similar to those of other types of reflex epilepsies (*i.e.* primary reading epilepsy), photosensitive epilepsy can be defined as an idiopathic epilepsy with age-related onset and a specific mode of precipitation (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

Differential diagnosis

The electroencephalogram (EEG), usually in the context of intensive video-EEG monitoring, remains fundamental in the investigation of reflex epilepsy. Intermittent photic stimulation (IPS) is standard in the performance of EEG recordings. Diagnosis confusion may arise due to the difficulty in evaluating epilepsies, in general, on the basis of the significance of the epileptiform reaction to IPS and, in particular, visually-induced seizures in daily life (Kasteleijn-Nolst Trenité *et al*, 1987). Another important consideration is the overlap in phenotype between the common juvenile myoclonic epilepsy and photosensitivity. About 30% patients with juvenile myoclonic epilepsy have a photoparoxysmal response (PPR) (see diagnostic methods) to IPS. Some progressive myoclonus epilepsies such as [Unverricht-Lundborg](#) or Baltic myoclonus and [ceroid lipofuscinosis](#) are also characterized by epileptiform reaction to IPS. These syndromes have been localized to different chromosomes (Berkovic *et al*, 1993).

Etiology

The etiology of photosensitive epilepsy is unknown. A family history of epilepsy is reported in a great majority of patients. This is in accordance with the common genetic background observed in idiopathic photosensitivity.

Clinical description

In visually sensitive patients, myoclonic or tonic-clonic seizures manifest typically at the age of 8-10 years; the risk of having visually-induced seizures then increases until after puberty, with a decline after the age of 25 years. Most patients (75%) have tonic-clonic, myoclonic, and absence seizures, whereas a minority (25%) have a history of partial seizures. Photosensitive patients typically have subtle eyelid myoclonic movements, jerks of the arms (mostly, symmetric), and massive jerks of the whole body. These signs occur with or without loss of consciousness and subjective symptoms.

Diagnostic methods

Photosensitive epilepsy diagnosis is based on subjective symptoms and clinical signs, EEG recordings in response to intermittent photic stimulation (IPS) or a combination of these. Photoparoxysmal responses (PPR), which are elicited by IPS, are classified into four different types according to the degree of generalization: type 1 - spikes within the occipital background activity; type 2 - parieto-occipital spikes with a biphasic slow wave; type 3 - parieto-occipital spikes with a biphasic slow wave and spread to the frontal region and type 4 - generalized spikes and wave or polyspikes and waves. Type 4 discharges are the most frequent finding sometimes associated with myoclonic jerks. In some patients, the epileptiform discharges can be accompanied by slight twitches of the upper extremities, the face or the eyes. Consciousness is rarely affected. Almost, all patients with PPR report sensations, usually for an unpleasant feeling ranging from horror to embarrassed laughter at being unable to control the jerking movement. Standard IPS procedure reported that photosensitive patients are most sensitive when photic stimulation is performed during eye closure (93%), they are less sensitive with their eye closed (81%), and they are least sensitive with their eye open (66%) (Kasteleijn-Nolst Trenité *et al*, 1999). Difference in prevalence rates can be explained by the different equipment used (difference in flash intensity, delivery of flashes, flash duration, or a combination of these), different stimulation conditions such as distance to the photic stimulator, continuous stimulation with increasing frequencies or separate trains of stimulation, one or more eye conditions (eye closure, eyes closed, or eye open), and ambient light levels. All these influence the outcome of IPS.

Epidemiology

In 1980, a prospective prevalence study was performed on 2 342 patients (Kasteleijn-Nolst *et al*, 1989). In an initial screening 5,6% appeared to be photosensitive, whereas 1,8% showed a reaction to IPS that did not meet criteria of a classic photoparoxysmal response. Two-thirds of the patients were girls and women between 10 and 25 years old. More than 90% of the patients with a PPR outlasting the stimulus train had a history of epilepsy, whereas a history of epilepsy was found in 84% of control subjects from the same EEG population matched for age, sex, and outpatient referral, without a PPR to IPS. In a German epileptic patient population of 1 000 subjects, about 4 000 EEGs were screened for spontaneous and IPS-induced discharges (Wolf, 1986). Ten percent appeared to be photosensitive.

In summary, an epileptiform reaction to IPS can be found in about 4% of normal children 6 years of age and older and in 0,5% to 5% of normal adults. The prevalence in epileptic patients is about 10% to 20% in children, and 5% to 10% in adults. Often, epileptic seizures are elicited by IPS. Females are more susceptible to IPS than males, with a peak age range of 12 to 18 years.

Genetics

Photosensitivity has been used as a genetic marker for epilepsy. Results of many genetic studies of photosensitivity suggest that the EEG response to IPS can be considered as a phenotypic expression of a genetically determined trait (Andermann *et al*, 1982). One problem in the investigation of genetic factors in photosensitive epilepsy is the attenuation or even the loss of the reaction to IPS with increasing age. In follow-up studies, the reaction to IPS in the laboratory is much diminished or abolished after the age of 25 years. Photosensitivity is a frequent EEG finding in idiopathic generalized epilepsy (IGE), thus genetic analysis of photosensitivity appear to be an important contribution to the genetics of IGE. Genetic studies of photosensitive epilepsies give support for an autosomal dominant mode of inheritance with age-dependent penetrance (Waltz *et al*, 2000).

Management and treatment

The presence of a clear triggering factor should lead to restrictions concerning exposure to the trigger. The indication of medical treatment with anti-epileptic drugs (AED) should be assessed on an individual basis according to the photosensitivity range of each patient. The prognosis in most patients ranges from good to excellent (Jeavons *et al*, 1986). Valproic acid (Depakine®) and a more recently marketed AED such as levetiracetam (Keppra®) suppresses the photosensitivity in the majority of patients, and after age 25, withdrawal of the medication is often possible. Lamotrigine (Lamictal®) and the benzodiazepines (Urbanyl®) are AEDs of second choice (Jeavons *et al*, 1975). The effect of topiramate (Epilex®) is not already established.

Unresolved questions

Whether the seizures in daily life are related to visual stimuli such as intermittent light stimulation (ILS) or pattern is difficult to establish. Sometimes one cannot determine whether a seizure was visually induced or whether it was spontaneous. The distinction between patient with pure photosensitive epilepsy and those with a combination of

spontaneous and visually-induced seizures is therefore artificial. Partial seizures can be triggered by simple or complex photic stimuli with no detectable cerebral lesion (Guerrini *et al*, 1995; 1998). This is another unrecognised phenomenon accounting for 2.5% of all photic-induced seizures (Jeavons *et al*, 1975). The focus here is in the occipital lobe and the presentation can mimic migraine.

Non-verbal and verbal induced epilepsies

Disease name and synonyms

- *Non-verbal induced epilepsy: praxis-induced seizures*
 - Thinking epilepsy
 - Emotional epilepsy
 - Reflex decision-making epilepsy
 - Epilepsy arithmetica (mathematica)
 - Writing or graphogenic epilepsy
 - Chess or card epilepsy
 - Eating epilepsy
- *Verbal induced epilepsy: language-induced epilepsy*
 - Reading
 - Speaking epilepsy
 - Writing or graphogenic epilepsy

Definition

Higher mental activities such as reading, speaking, writing, talking, calculating, concentrating, playing chess, reading music or playing piano have been reported as triggering focal or generalized epileptic seizures, termed "reflex seizures". Seizures triggered by non-verbal higher brain activities relating to spatial processing and ideation or movements are considered as "praxis-induced seizures" (Gossens *et al*, 1990; Inoue *et al*, 1994) whereas those precipitated by verbal processing are classified as language-induced epilepsy (Geschwind and Sherwin 1967; Bennett *et al*, 1971; Lee *et al*, 1980). This last subgroup includes seizures provoked by reading, either silently or aloud (Bickford *et al*, 1956), by speaking (Marchini *et al*, 1994) or writing (Asbury and Prenskey 1965; Tomohiro *et al*, 2003). Seizures triggered by thinking or by emotion are more specifically induced by spatial tasks, chess, playing cards and decision-making (Ingvar and Nyman 1962; Wilkins *et al*, 1982). Seizures induced by eating may occur at the sight or smell of food, at the beginning of eating a meal or postprandially (Nagaraja and Chand, 1984). Non-verbal and verbal-induced epilepsies may be divided into epilepsies that are primary or idiopathic (with a genetic basis) and epilepsies that are secondary or symptomatic

(with an acquired basis). Primary reflex seizures are precipitated by one and only one stimulus and occur under no other circumstance. Secondary seizures are induced by several triggers and spontaneous seizures occur.

Differential diagnosis

Clinical pattern, genetic and EEG recordings are overlapping in several idiopathic epileptic syndromes, particularly those developing and witnessed during adolescence (Reutens and Berkovic 1995).

EEG findings and clinical seizures in reflex seizures provoked by intellectual activity such as praxis or decision-making are often reminiscent of those observed in idiopathic generalized epilepsies with an age-related onset, such as [juvenile myoclonic epilepsy](#) (JME) or [benign epilepsy with centro temporal spikes](#) (BECRS). Age at epilepsy onset, family and personal history of seizures do not differ from those of JME patients who do not have reflex seizures. If isolated jerks occur without leading to myoclonic jerks, ictal disturbance of spoken language, or a generalized convulsion, the condition may not be recognized as a form of epilepsy. Isolated jerks may be dismissed as a meaningless tic and associated ictal language disturbance may be ascribed to stuttering or to a movement disorder.

Etiology

The etiology of non-verbal and verbal-induced seizures is unknown. Such reflex seizures are rare and are sometimes very difficult to diagnose.

Clinical description

In predisposed individuals, reflex epilepsies can trigger a generalized epileptic process with both minor (myoclonus) and major attacks (generalized tonic-clonic seizure). The clinical hallmarks of these reflex seizures are abnormal sensations or movements (tonic or myoclonic) of musculature involved in complex trigger performance. Patients reported episodes of abrupt, involuntary, isolated hemifacial or limbs jerks. Verbal-induced epilepsies are associated with a subjective sensation of clicking, mouth trembling, stuttering, difficulty in pronouncing words and eventual speech arrest that may progress to a generalized tonic-clonic seizure (GTCS) if the stimulus persists. Concentration of attention or stress may contribute to the precipitation of seizures. The latency of seizure occurrence is influenced by many non-specific factors such as sleep deprivation, fatigue, alcohol intake and menstruation. Patients often recognize the initial symptoms and avoid

prolonged exposure to the stimulus to prevent GTCS.

Diagnostic methods

Diagnosis is based on clinical and electrophysiological criteria. Video-EEG recording is a critical test to elucidate the clinical and EEG features of the induced seizures and the modalities of their precipitation. Familial and personal history of the patient may report factors, which are likely to provoke jerks, and using these, events can often be elicited and recorded. In some patients, specific neuropsychological tasks induced EEG abnormalities, correlating with clinical manifestations. Execution of complicated movements, rather than simple ones, is prone to elicit clinical seizures. Video-polygraphic recordings show often-normal resting EEG background activity and sometimes interictal focal or generalized abnormalities. Ictal EEG findings have been found to vary widely, both in terms of morphology and topography (focal or generalized), in spite of the rather uniform clinical correlates. Surface EMG performed simultaneously during EEG recording allows confirming the concomitant occurrence of myoclonic jerks and epileptic activity.

Despite their obvious variability, ictal EEG recordings are used to as a major criterion as to whether reflex epilepsy is a localization-related or a generalized syndrome (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). The recognition of the triggering factors is very important to provoke reflex seizures and to become seizure-free.

Epidemiology

Non-verbal and verbal-induced epilepsies are unusual and often may be underdiagnosed. The incidence and prevalence are unknown.

Genetics

Non-verbal (praxis-induced) or verbal-induced seizures represent an inherited trait of seizures precipitated by specific modes of activation occurring mainly within idiopathic focal or generalized epilepsies (Matsuoka *et al*, 2000). Genetically, a distinct predisposition for a specific group of stimuli may be found. A family history quite often may be investigated. Dominant mode of inheritance is sometimes suggested (Daly et Forster, 1975).

Management and treatment

Therapy of reflex seizures involves limiting exposure to the provoking stimulus, as well as antiepileptic drugs. Antiepileptic drugs are

selected on the basis of idiopathic or symptomatic origin of the patient's seizures. Valproate, clonazepam and zonisamide are the most effective drugs in idiopathic forms.

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