The Photoparoxysmal Response: The Probable Cause of Attacks During Video Games

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ABSTRACT

Photic stimulation is part of a typical EEG in most countries, especially to check on the photoparoxysmal response (PPR). Interest in this response was enhanced in 1997 when hundreds of Japanese children had attacks while viewing a TV cartoon called "Pokemon." The overall prevalence of the PPR among patients requiring an EEG is approximately 0.8%, but 1.7% in children and 8.87% in patients with epilepsy, more often in Caucasians and females. Autosomal dominant inheritance is indicated, and this response is seen especially at the wavelength of 700nm or at the flicker frequency of 15-18 Hz. The PPR extending beyond the stimulus carries no increased risk of seizures. Prognosis is generally good, especially after 20 years of age. Attention to PPR has been increased with the advent of video games, and the evoked seizures from these games are likely a manifestation of photosensitive epilepsy. Drug therapy has emphasized valproic acid, but Levetiracetam has also been successful in eliminating the PPR.

INTRODUCTION

As part of a routine electroencephalogram (EEG) in most laboratories photic stimulation is included to check on asymmetrical photic driving responses, but especially to determine if photoparoxysmal spike and wave complexes are elicited. Therefore, most EEGers have considerable interest in these latter epileptiform complexes, as do epileptologists. Interest in the photoparoxysmal response (PPR) was very much enhanced on December 16, 1997, when hundreds of Japanese children had various types of attacks while watching an animated TV cartoon program with flickering red lights, call Pokemon – the "Pocket Monster."[1] Further interest, especially among clinical neurophysiologists, came from data from certain baboons who have demonstrated photosensitivity (PS). For example, among the Papio (hamadryas anubis) baboons, 50% showed generalized epileptiform discharges and 30% had actual seizures during photic stimulation.[2] In another related study from the same laboratory, among 100 baboons 67% showed generalized discharges and 40% had clinical seizures during flickering lights.[3]

TYPES OF PHOTOSENSITIVITY

According to Spread of Epileptiform Activity

In 1992 Waltz et al[4] described 4 different types of PS according to the spread of epileptiform activity. Type 1 consisted of only occipital (O) rhythms. Type 2 referred to parieto-occipital spikes with a biphasic slow pattern, while Type 3 was the same as Type 2 except it spread to the frontal areas. Type 4 is the one that most investigators have studied and consists of irregular generalized spike and wave complexes, seen more often both in probands with epilepsy and also their siblings than in respective controls. The same authors, Waltz et al,[4] considered that the varied patterns of the PPR represented different levels of expression of the same genetically determined trait.[5]

Photosensitive Occipital Lobe Epilepsy

In 1995 Guerrini et al[6] described visually induced O seizures, involving elementary visual symptoms, headache, abdominal pain, nausea and vomiting. These latter symptoms were difficult to differentiate from childhood epilepsy, described in 1982 by Gastaut.[7] In 1999 Harding and Fylan[8] contrasted the generalized PPR and the focal O spikes. They claimed that the PPRs and not the O spikes were dependant on linear contrast and were elicited by stationary, noncolor stimuli. The former (PPR) were viewed as generated by the parvocellular visual system and the latter (O spikes) by the magnocellular system

The same kind of symptoms mentioned by Guerrini were also described by Hennessy and Binnie,[9] who added deja-vu and auditory hallucinations to the list of symptoms for this partial type of attack. The equivalent dipoles of these seizures were judged as located in the O and inferior temporal cortices.[10] A few more details were added by Doose et al,[11] describing these patients with a typical age of onset < 5 years, often with a history of febrile seizures and generalized spike and waves in the resting EEG. Using transcranial magnetic stimulation other investigators[12] determined that the propagation of PS was associated with increased excitability of the O, but not the motor cortex.

Other Focal Partial Responses

The majority (65%) of patients with PPR also have had spontaneous epileptiform abnormalities,[13] more often generalized (36%) than focal (24%). As expected, those with focal discharges usually had partial seizures.

Temporal lobe

In 3 PS patients a "telephilic syndrome" was named for an impulsive attraction to television,[14] and the predominant area of

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epileptiform brain activity was the right midposterior temporal area. (It is interesting that on June 25, 2007, the headline in the Chicago Tribune was that AMA is considering that video games may be actually addictive to some individuals.) Other investigators[15] have designated a PPR patient with "photo-induced temporal lobe epilepsy," who had a change in consciousness during photic activation. Fiore et al[16] summarized their own view of 3 types of PPR: (1) the most common, generalized spike and waves, (2) the focal O discharges, but also (3) those originating from the temporal lobe. In a patient in category 3 an interictal SPECT scan confirmed a hyperperfusion within the right temporal lobe, and a lobectomy of that lobe rendered that patient seizure free.

Central Rolandic Area

In some patients with PPR, multifocal sharp wave foci were seen at times in the resting EEG, especially on the central areas, indistinguishable from those with Rolandic epilepsy and called "atypical benign partial epilepsy of childhood."[17]

Typical Generalized Spike and Wave Complexes

The classical PPR to intermittent photic stimulation has been frequently investigated. As early as 1987 investigators[18] reported that 75% of patients with PPR experienced impaired consciousness and/or motor phenomena, such as involuntary opening of the eyes or jerking of the body. The evidence in Japan for the PPR was 1.7% in patients with epilepsy with a mean age of 17 years, but accounting for only 6% of idiopathic generalized epilepsy, and 17% of juvenile myoclonic epilepsy (JME). The prevalence increased up to 15 years of age and then decreased after age 20 years.[19] The PPR was less variable with photic stimulation than the spontaneous epileptiform activity that often appeared, but usually those complexes were responsive to antiepileptic drugs.[20] Other investigators[21] have emphasized that the PPR was not a marker for clinical epilepsy. In 30% of the nonepileptic patients the response was lost in 1-6 years, but in 70% they continued to be present. However, a review in 2004[22] emphasized the presence of PPR during adolescence, although lessening later, most often was associated with generalized epilepsy, especially in JME, and with an important genetic factor.

PREVALENCE OF PPR

Nearly one half of a century ago, the present reviewer reported that 3% of all patients seen in his EEG laboratory included the PPR.[23] Almost 50 years later these photically induced epileptiform complexes have become so rare that their presence represents an important occasion in his present laboratory. Thus, the suggestion is that the prevalence is diminishing over time. Evidence in favor of this suggestion comes from South Africa and Zimbabwe where the prevalence values were taken in different years. For example, the prevalence among Caucasians with epilepsy was 5.2% in 1992,[24] 2.7% in 1995[25] and 1.5% in 1998.[26] Comparable values for the mixed race were 4.2% in 1992, 0.9% in 1995 and 0.4% in 1998. For black Africans the values were 0.4%, 0.1% and 0.1%, respectively. Speculation would be that habituation of some type has occurred over time; television and/or computer games may well be involved.

The prevalence of PPR among those having an EEG was 0.5%[27] or 0.8%,[26] 1%[28] and 1.35%[29] or 2.0%[26] in children. Among those with epilepsy the values were 1.7%[19] or 2%.[30,31] Thus, in studies mainly after 2000 approximately 0.8% was the prevalence for those of any age having an EEG, 1.7% specifically in children and 1.8% in patients with clinical seizures. One outlier among these values was the 8% reported by one group as the prevalence in children having an EEG in 2003.[32]

VARIABLES OF PPR

Individual

Race

As noted in the previous section, Prevalence of PPR, Caucasians (whites) with epilepsy in 1992 showed a PPR at 5.2% compared to 4.2% in the mixed race and 0.4% in blacks[24] with similar differences in later years.[25,26] Consistent data from another study was 2.5% (whites), 1.3% (mixed) and 0.9% (blacks), respectively.[33] In addition, consistent data of the PPR also comes from a 53% prevalence of British patients with generalized tonic-clonic attacks, in contrast to only 16% of patients in Nigeria.[34] In this latter study the speculation was that the larger amount of sunshine in the tropics could explain the relatively low incidence of PPR among the blacks in Africia.

Gender

The prevalence of the PPR was 75% in females,[35] nearly the same as the 72% in another study.[36]

Age

One study indicated that the mean age for the PPR was 12 years,[37] consistent with the ages of 7-19 years as the stated highest prevalence of those with seizures.[30] These data explain why other investigators have determined that the genetic transmission of the PPR was maximal in its penetrance between 5 and 15 years.[37]

Eye Closure

In one study the PPR was seen best at the moment of eye opening or eye closure,[14] while another investigation showed that in 53% the response was mainly with eye closure.[38]

Inheritance

As early as 1993 Doose and Waltz[5] concluded that available data provide evidence for autosomal dominant inheritance of PS. They also indicated that the phenotypical expression of the PPR was determined by other pathogenetic factors related to epilepsy. Seven years later in 2000 two different groups were studied by Waltz and Stephani[39] each with a photosensitive proband. Group I had one photosensitive parent and Group II did not. Seizures occurred in 33% (I) and 9% (II). Group I showed a 50% prevalence of PPR in the siblings, compared to 15% in Group II, and seizures in those siblings appeared in 19% (I) and 4% (II). These results were viewed as indicating an autosomal-dominant transmission. The same conclusion was drawn from investigators from the same laboratory 4 years later[22] and also from a different group and from a different laboratory.[37]

Stimulus Conditions

Frequency of flicker

Based on experience, the present reviewer would emphasize that the most effective flicker frequencies have been multiples of 3, possibly because the basic frequency of the (irregular) bilateral spike and wave complexes is usually near 3/sec. Therefore, the conclusion of Topalkara et al[40] that 15-18 Hz was the most epileptogenic is consistent, as is the 18 Hz mentioned by another group[41] or the 15-20 Hz[42] or 20-24 Hz[35] from other investigators. The red-blue alternating colors were used at the frequency of 12 Hz by 2 different Japanese groups after the Pokemon event.[43,44]

One last example of the frequency question was explored in the Netherlands[36] contrasting the use of the 50 Hz TV vs 100 Hz TV eliciting PPRs in PS patients in 57% vs 41%, respectively. These latter results suggest that countries (UK) using 50 Hz as their main frequency may have more epileptiform responses from TV viewing than in countries (USA) with higher frequencies, like 60 Hz.

Luminance

One group explored the effect of various sunglasses on the PPR and concluded that the suppressive effect of these glasses was mainly due to a luminance diminution.[45] Thus, it was low luminance that was effective in suppressing the PPR. On the other hand, it was low luminance that produced PPR, seen in various reports.[41,46,47] However, other investigations have reported that PPRs are found only above a certain luminance.[48,49] Thus, there is a controversy about whether a relatively low or high luminance is required to elicit a PPR with more reports emphasizing low luminance.

Wavelength

As early as 1995 investigators designated the wavelength spectrum of 700 nanometers (nm) as the only visible spectrum essential for eliciting the PPR. If this spectrum was filtered out, no PPR occurred.[50] Two years later the same group confirmed this point.[51] Others have made the same point by stating that deep red color is required for the stimulus to elicit the PPR.[52,53] These data led to the conclusion of Takahashi et al[49] that some PPRs are dependant on wavelength, but the authors added that others depend on quantity of light. This conclusion was confirmed in 2001 that there are two types of pathophysiological mechanisms for PPRs and they are wavelength dependant and quantity of light dependant.[54]

The emphasis on the importance of red light led to studies to inhibit this effect, and Takahashi was likely the leader in this effort. He and Tsukahara[45] demonstrated that blue glasses eliminated the PPR and speculated that these sunglasses produced an inhibitory effect of short wavelengths and also possibly by an illuminance diminution.[45] Others have confirmed the effect of the blue lens.[54-56]

Season Variation

Especially because blacks in sunny Africa showed fewer PPRs than whites from colder and cloudy climates,[34] some have speculated that in the summer a decrease in PPR may occur compared to the winter time when a decrease in sunshine often occurs.[57] However, Quirk et al[30] found no difference in the incidence between summer and winter. Another group[58] reported that only 0.6% of North Indian epilepsy patients showed the PPR, in contrast to 3.5% for the South Indian patients. Their conclusion was that environmental and racial factors cannot explain this difference, and that age, gender, epilepsy type, sleep deprivation, technique of stimulation and the definition of the PPR greatly influence these prevalence rates. Seven years later the same general point was made by another investigator.[27] The same investigator, Trenité,[59] has emphasized the need to standardize studies to deal with all of the relevant variable in the PPR.

SEIZURES ASSOCIATED WITH PPR

Patients vs Normals

One study with 48 normal subjects and 3,557 patients each requiring an EEG found that none of the normals showed PPR and only 1% of the patients had such a response.[60] Of the latter patients 77% of them had a definite history of epilepsy and an additional 9% had a questionable history of seizures.

Single Seizures vs Many Seizures

Another study compared patients who had had only one attack vs those diagnosed with epilepsy with multiple attacks and reported no significance difference in the prevalence of the PPR at 6.4% vs 5.9%.[61]

Symptoms during PPR

As previously mentioned in the "Typical Generalized Spike and Wave Complexes" section on page 2, during the intermittent photic stimulation 75% of the patients with a PPR experienced impaired consciousness or showed motor phenomena, such as involuntary opening of the eyes or jerking on one or both sides of the body.[18] In 69% there were sensations such as pain in the eyes, and in nearly one third these latter symptoms had not been previously mentioned by the patients or their relatives.

Prevalence of Seizures in Patients with PPR

In three fourths of patients with a PPR, clinical seizures were reported in the history and in nearly one half the resting recordings showed generalized spike and wave complexes.[35]

PPR during Alcohol Withdrawal

Since generalized seizures may occur during alcohol withdrawal, the expectation could be that the PPR as a generalized discharge may be found in the state. However, Fisch et al[62] never found the PPR in his group of 49 patients in withdrawal.

Limited vs Extended PPR during Stimulation

One question was whether the PPR occurred only during the photic stimulation or extended beyond the end of the stimulation, as a possible indication of the severity of the condition. Puglia et al[63] reported that in the latter condition a higher incidence of seizures appeared, and also other epileptiform abnormalities were found in the resting record than in the group with the self-limited PPR. When comparing these two groups with regard to other epileptiform abnormalities, in the resting record then there was no difference in seizure incidence. Thus, the presence of the other abnormalities in the EEG and not the PPR extending beyond the end of the stimulus was the significant factor for seizures. Confirmation of this general point came from another study that reported the persistence of the PPR beyond stimulation was not associated with a higher risk of clinical seizures.[64]

PROGNOSIS

For prognosis, age has been known to be important since a number of investigators have reported an increase in PPR during adolescence and a definite decrease after 20 years of age.[19,22,65] Also, those without previous seizures understandably had the most favorable prognosis.[66] The disappearance of the PPR in children occurred in 1-5 years in nearly 39%,[21] and in 5-12 years in 60% and 79% were seizure free at that time. For the Japanese investigators who studied seizures associated with the "Pocket Monster," recurrence of seizures occurred in only 27% in 5 years.[66] Thus, in general, prognosis was favorable.

ASSOCIATION OF PPR WITH CHROMOSOMES AND VARIOUS DISORDERS

Enzyme Deficiency

Succinie semialdehyde dehydrogenase deficiency (SSADH) is a neurometabolic disorder characterized by seizures, including absence and myoclonic attacks and also the PPR,[67] Confirmation of the PPR in this latter condition came from another group,[68] reporting on the gene likely involved (ALDH5A1), associated with chromosome 6p22.

Genes Involved in PPR

In 2005 a group identified two susceptibility loci for the PPR and they were chromosomes 7q32 and 16p13.[69] Another group reported a locus on 6p21.2 that was said to predispose to the PPR, whereas the locus on 13q31.3 was thought to confer susceptibility to idiopathic generalized epilepsy, often associated with the PPR.[70] More recently in 2006, confirmation was reported that the PPR was mapped to the chromosomal region of 6p21.[71] Also, evidence was presented that the genetic variation of BRD2 was the underlying susceptibility gene. Even more recently in 2007, Pinto et al[69] concluded that the two susceptibility loci for the PPR were, as previously indicated, at regions 7q32 and 16p13, likely acting on the same biochemical pathway.[72]

Migraine

The PPR has been investigated in patients with migraine, seen in 7.8% with aura, 8.9% without aura, compared to 6.7% with only tension headache, thus, without any significant difference.[29] When children with migraine with aura under 12 years old were studied, then 18% had the PPR. In 12% the PPR was generalized and in 6% they were localized on the temporal parieto-occipital region. In nearly one half of the patients with migraine and PPR, photogenic stimuli were the most frequent provoking factor for their migraine attacks. One conclusion was that these data support the theory about general cortical hyperexcitability in migraine.

Unverricht-Lundborg Disease

In 20 patients with this disease, symptoms included myoclonus, seizures and the PPR. These patients were followed for an average of 26 years and the PPR had disappeared by that time in all patients.[73] Confirmation of these results can be found in 25 other patients. PPR was found in 88% at disease onset but gradually disappeared after 10 years.[74]

Eyelid Myoclonia with Absence (EMA)

In this disorder generalized polyspike wave discharges appeared right after eye closure and also PPR was found.[75]

Chromosomal Aberrations

In 28 patients with various chromosomal aberrations 14% showed the PPR indicating a higher risk for photosensitivity.[76]

PPR AND VIDEO GAMES

An early report in 1994[77] showed that over one half who had seizures during video games also showed a PPR. The seizures were usually generalized. This relationship between seizures and PPR was explored by investigating 118 patients who had their first seizure mainly at 7-19 years of age while playing a video game and determining how many showed a PPR. Quirk et al[78] reported that nearly 40% had a definite PPR and a probable response was seen in 20% so that 60% showed such a relationship.

The relationship was further explored in another study,[79] comparing patients with seizures during video games vs those with photosensitive epilepsy, but with no video game attacks. The results showed no differences elicited by various stimuli, suggesting to the investigators that video games' seizures were likely a manifestation of photosensitive epilepsy.

One other study reported similar clinical signs during video games or intermittent photic stimulation or striped patterns, suggesting similar mechanisms involved with video game attacks and PPR.[80]

One last report was designed to place many of these results in perspective, and the conclusion was that the modern technological environment has led to a dramatic increase in exposure to potential trigger stimuli.[37] Although one supposition would be that more seizures and more PPR would be forthcoming, some data would suggest that habituation to these many visual stimuli has occurred and the prevalence of the PPR has actually diminished (see section Prevalence of PPR).

SPECIAL STUDIES

Functional Magnetic Resonance Imaging (fMRI) and Magnetic Resonance Spectroscopy (MRS)

In one study[61] of fMRI, abnormalities were found while the PPR occurred, but photosensitive patients showed 4 unique findings, compared to normals: (1) increased lactate levels in the O cortex during the resting state, (2) increased areas of visual cortical activation with photic stimulation, (3) with the increase of fMRI signal in the O cortex attenuation was seen in perirolandic areas and (4) a marked decrease of MRI signal in the O cortex after the photic stimulation. These data suggested abnormal interictal metabolism and increased vascular reactivity in photosensitive patients. The exact same study was reported in a Supplement with a different arrangement of authorship.[82]

Position Emission Tomography (PET)

During the PPR these patients showed an increase in regional cerebral blood flow (rCBF) in the hypothalamic region, inferior to the caudate nucleus.[83] Without the PPR but during photic stimulation, an increase in rCBF appeared in the head of the left caudate nucleus, on the left hippocampus and insula. These data indicate an involvement of the hypothalamus and caudate nucleus during photic stimulation.[83]

Visual Evoked Potentials

One study showed in photosensitive patients that the P100 had normal latencies, but higher amplitudes.[84] These higher amplitudes in evoked potentials have been well known in patients with epilepsy, especially with somatosensory evoked potentials.[85]

Gamma Band

Parra et al[86] reported that an enhancement of phase synchrony in the gamma band (30-120 Hz), harmonically related to the frequency of stimulation, preceded the stimulation trials that evolved into the PPRs. One postulation was that a pathological deviation of normally occurring synchronization of gamma oscillation may mediate the epileptic transition in photosensitive epilepsy.

Equivalent Current Dipole

One study dealt with the location of the electrical generator of the PPR and concluded that neural activity of the lateral geniculate body might be responsible for the generator mechanism associated with photosensitive epilepsy.[67]

DRUG THERAPY

Anti-Epileptic Drugs (AEDs)

Sodium valproate (VPA)

Among 100 patients with photosensitive epilepsy and a follow-up of 27 years 54 were treated with VPA and 43% had no more PPR, in contrast to an untreated group with only 50% without the PPR. Although VPA controlled some patients, 63% of all patients (treated and untreated) showed a persistent PPR.[88] Another group[37] concluded that the majority of patients do not need AEDs, but, if needed, VPA was the drug of choice. On the other hand, children with chromosomal anomalies rarely were controlled by AEDs.[76] One last study involved VPA and at times combined with other AEDs. After 5-12 years follow-up 60% had lost their PPRs suggesting a good prognosis, especially because 79% were seizure free.[65]

Levetiracetam (Lev)

As early as 1996, long before this AED was approved in USA, a study was conducted in the Netherlands, demonstrating abolishment of the PPR in 50% and suppression in an additional 25%. Abolishment was seen at 750mg and 1000mg per day.[89]

Brivaracetam

As a "relative" to Levetiracetam this new AED, with a binding 10 times (re LEV) the affinity to synaptic vesicle 2A (SV2A), demonstrated that the PPR was abolished or reduced at all tested dosages (10-80mg).[90]

Piracetam

As early as 1991 this medication, not ordinarily used as an AED, but considered as a possible stimulant for demented patients, showed that all 3 patients had their PPR eliminated at doses up to 10g/day.[91]

Loreclezole

One group studied this new AED and reported that 100-150mg resulted in a decreased photosensitivity in all patients tested.[92]

Carisbamate

This novel neuromodulatory drug resulted in a dose dependent reduction in PS in 72% of patients. When 1000mg were given sensitivity was abolished in all 5 patients.[93]

SUMMARY

Photic stimulation is part of a routine EEG in most laboratories in the world, especially to check on the photoparoxysmal response (PPR) as bilateral generalized spike complexes. Interest in this response was very much enhanced on December 16, 1997, when hundreds of Japanese children had attacks while viewing on TV the cartoon Pokemon, the "Pocket Monster." The PPR was differentiated from photosensitive occipital epilepsy with O spikes, focal discharges on the temporal lobe and also on the central areas. The PPR itself was seen, especially in juvenile myoclonic epilepsy, mainly during the teens. The overall prevalence of the PPR in patients having an EEG is approximately 0.8%, but 1.7% in children and 1.8% in patients with epilepsy, but is likely diminishing over time. Evidence has appeared that there is a higher prevalence in Caucasians, in females and in children and adolescents. Data indicated an autosomal dominant inheritance for photosensitivity (PS), which appears especially with a wavelength spectrum of 70nm or at flicker frequencies of 15-18 Hz at low luminance, inhibited by blue sunglasses but without seasonal variation. Normals usually show no PPR, but in the 1% of patients having an EEG three fourths of them have had a history of seizures. During the photic stimulation three fourths experienced impaired consciousness or motor phenomena and one half showed generalized paroxysms in the resting record. The PPR extending beyond the stimulus is not associated with a higher risk of seizures. Prognosis has generally been good, especially after 20 years of age with seizure freedom in 79% after 5-12 years. Inheritance has been clear for the PPR, but, as in other types of the epilepsy controversy, has appeared as to the chromosomes involved. Evidence is seen for the susceptibility loci as 6p21, 6p21.2, 7q32, 12q31.3 and 16p13. A relationship has appeared between PPR and migraine, Unverricht Lundborg Disease and Eyelid Myoclonia with Absence.

Attention to PPR has been enhanced with the advent of video games since evoked seizures from these games are likely a manifestation of photosensitive epilepsy. Although no fMRI changes were seen during the PPR, increase in lactate in the O areas and decrease in MRI signal were seen in the perirolandic areas. PET scans have shown increased regional cerebral blood flow in the hypothalamus. The visual evoked potential showed an increased amplitude in the P100, an increase phase synchrony occurs in the gamma band and the equivalent current dipole for the PPR is likely within the lateral geniculate body. Drug therapy has emphasized valproic acid, but Levetiracetam has also been successful in eliminating the PPR. Although less common than in the past, the PPR still needs to be identified with an EEG so appropriate medication can be given to the many patients with this pattern.

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