Seizure: European Journal of Epilepsy 64 (2019) 1–5

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Ictal piloerection is associated with high-grade glioma and autoimmune encephalitis—Results from a systematic review

Dalma Tényi[a], Beáta Bóné[a], Réka Horváth[a], Sámuel Komoly[a], Zsolt Illés[a,b], Christoph P. Beier[b], Anna Kelemen[c], Norbert Kovács[a,d], Gergely Darnai[a], József Janszky[a,d,*]

[a] Department of Neurology, University of Pécs, H-7623, Rét u. 2., Pécs, Hungary
[b] Department of Neurology, Odense University Hospital, Odense, and Department for Clinical Research, University of Southern Denmark, Odense C, DK-5000, Winsløwparken 19, Denmark
[c] National Institute of Clinical Neurosciences, H-1145, Amerikai út 57, Budapest, Hungary
[d] PTE-MTA Clinical Neuroscience MR Research Group, H-7623, Rét u. 2, Hungary

ARTICLE INFO

Keywords:
Piloerection
Autonomic nervous system
Autonomic seizures
Focal epilepsy
Temporal lobe seizures

ABSTRACT

Purpose: To comprehensively analyze ictal piloerection (IP) in a large number of subjects.
Methods: We performed a systematic review on case report studies of patients diagnosed with IP (1929–2017) with additional cases included from the Department of Neurology of University of Pécs, the National Institute of Clinical Neurosciences, and Odense University Hospital. Each included case was characterized regarding patient history, IP seizure characteristics, diagnostic work-up, and therapy. Comparative analyses were also carried out based on sex and pathology.
Results: Altogether, 109 cases were included. We observed a strong male predominance ($p < 0.001$). The mean age at onset of epilepsy was 39.5 ± 20.7 years (median: 38, IQR:24–57). The seizure onset zone was temporal ($p < 0.001$), and was lateralized to the ipsilateral hemisphere in unilateral localization ($p = 0.001$). The seizure was accompanied by cold shiver in 53%, and by other autonomic symptoms in 47% of cases. In 53% of patients, IP never progressed into complex partial or generalized tonic-clonic seizure; 16% of the patients reported occasional, and 31% regular generalization. Seizure frequency was higher among females (median:25/day, IQR:3–60) than among males (median:3/day, IQR:1–11) ($p = 0.017$). The two most common underlying pathologies were limbic encephalitis (23%) and astrocytoma (23%, among them 64% WHO III-IV astrocytoma).
Conclusion: IP was particularly associated with autoimmune encephalitis and high-grade glioma, suggesting IP's particular clinical importance in directing diagnostic work-up.

1. Introduction

Autonomic changes during epileptic seizures are well-established phenomena. Cardiorespiratory symptoms are the most prominent: tachycardia, facial flushing, hyperventilation and apnoe usually accompany complex partial and generalized tonic-clonic seizures, especially those of temporal lobe origin [1]. In our previous study, we recorded at least one vegetative sign in 86% of the patients with temporal lobe seizures [2]. These symptoms are probably directly caused by the epileptic activity of the central autonomic network [3]. In case of focal autonomic seizures, the autonomic symptoms dominate the clinical picture, although this seizure type is much less common. Ictal piloerection (IP) has been described as an accompanying, as well as a prominent seizure symptom, and its prevalence among epilepsy patients is estimated to be 1.2% [1]. The exact pathomechanism is still debated. According to stimulation experiments, several parts of the brain have been suggested as the symptomatogenic zone: the insula, hippocampus, amygdala, hypothalamus, medial prefrontal cortex, parahippocampal and cingular gyrus [3]. Ictal piloerection has been described mainly in case reports and small case series. Analyzing 16 patients with cold shiver (n = 11) and ictal piloerection (n = 4), Stefan et al. [4] suggested left temporal lobe origin. Loddenkemper et al. analyzed the localizing and lateralizing value of ictal piloerection in 14 patients, who were diagnosed with ictal piloerection [3]. They found that ictal piloerection was associated with temporal lobe seizure onset zone. Regarding lateralization, only IP with unilateral onset showed lateralizing value, being ipsilateral to the seizure onset zone [3]. Based on 5 patients, a recent study suggested that IP was associated with limbic

* Corresponding author at: Department of Neurology, University of Pécs, H-7623, Rét u. 2., Pécs, Hungary.
E-mail address: janszky.jozsef@pte.hu (J. Janszky).

https://doi.org/10.1016/j.seizure.2018.11.009
Received 26 July 2018; Received in revised form 15 November 2018; Accepted 18 November 2018

Table 1
Data of patients with autoimmune etiology.

Patient	Symptoms (N.O.)	Antibody	CSF	Neuroimaging (MRI)	Tumor
Definite limbic encephalitis					
1	seizures, memory deficit	Ma2 (CSF)	unknown	right HS	testicular cancer
2	seizures, dysexecutive syndrome	LGI1 (CSF + SE)	unknown	right HS	unknown
3	seizures, dysexecutive syndrome	LGI1 (SE)	unknown	swelling of left amygdala, hippocampus	unknown
4	seizures, memory deficit	Hu2 (CSF)	unknown	left HS	–
5	seizures, memory deficit	LGI1 (SE)	unknown	bilateral temporal hyperintensity	unknown
6	seizures, memory deficit	VGKC (SE)	pleocytosis, increased protein	bilateral temporal hyperintensity	–
7	seizures, memory deficit	VGKC*	unremarkable	bilateral hippocampal hyperintensity	–
8	seizures, memory deficit	LGI1 (SE)	unremarkable	left mesial temporal hyperintensity	–
9	seizures, dementia	VGKC (CSF)	VGKC antibodies	FDG-PET: low FDG uptake in the frontal and temporal lobes	cholangiocarcinoma
10	seizures, memory deficit	UNK**	oligoclonal gammopathy	bilateral mesial temporal hyperintensity	–
11	unknown	$GABA_BR$ (unknown)	unknown	unknown	unknown
12	seizures	NMDA (SE)	oligoclonal gammopathy	normal	–
13	seizures, memory deficit	GAD (CSF, SE)	oligoclonal gammopathy	right mesial temporal atrophy	–
14	seizures	GAD (CSF, SE)	pleocytosis, increased protein	normal	–

Patient	Symptoms (N.O.)	Antibody	CSF	Neuroimaging (MRI)	Tumor	Other
Possible limbic encephalitis						
15	seizures, memory deficit, psychiatric symptoms	–	increased protein	normal	–	–
Suspective of autoimmune origin***						
16	–	CASPR2 (SE)	–	left HS	–	chronic epilepsy, comorbid depression
17	–	GABAaR (SE)	–	right HS	–	chronic epilepsy, comorbid depression
18	seizures	–	unknown	right mesial temporal swelling, then atrophy	–	sequential MRI changes
19	seizures	–	increased protein	right mesial temporal swelling, then atrophy	–	sequential MRI changes
20	seizures	was not tested	was not tested	left mesial temporal swelling, then atrophy	–	sequential MRI changes
21	–	GAD (unknown)	unknown	normal	–	comorbid depression
22	–	NMDA (unknown)	was not tested	normal	–	comorbid depression
23	–	VGKC (unknown)	was not tested	normal	–	comorbid depression

Caspr2: contactin associated protein receptor 2; **CSF**: cerebrospinal fluid; **FDG-PET**: fluordesoxyglucose positron-emission tomography; **$GABA_BR$**: gamma-aminobutyric acid B receptor; **GAD**: glutamic acid decarboxylase; **HS**: hippocampal sclerosis; **LGI1**: leucine-rich, glioma inactivated 1; **MRI**: magnetic resonance imaging; **NMDA**: N-methyl-D-aspartate receptor; **N.O.**: new onset; **SE**: serum; **VGKC**: voltage-gated potassium channel.
*: appeared only later, and unknown whether it was present in serum and/or CSF; **: negative to NMDA, GAD, $GABA_A$, $GABA_B$, LGI1, AMPA, Caspr2, Ma2, Ri, Yo, Hu, CV2; ***: but neither definite, nor probable, nor possible limbic encephalitis could be established.

encephalitis (LE) [5].

In our study, we aimed to examine whether IP is associated with particular etiologies. By analyzing a high number of patients, we were able to perform comparative statistical analyses beside descriptive studies in order to describe the clinical characteristics of IP and the epilepsy that is associated with IP.

2. Methods

2.1. Search strategy

We performed (i) a systematic review from the first date available (1929) to May 2018. PubMed and Scopus were searched for case reports, case series, reviews and abstracts, using the search term "pilomotor" and "piloerection" with the following prefixes: "ictal", "seizure" and "epilepsy". (ii) We also searched among patients admitted for presurgical evaluation at our video-EEG monitoring units between 2007 and 2017 (n = 512) the diagnosis of IP. Patients were included if IP was an accompanying symptom in an epileptic seizure, or if IP appeared as the only symptom of the seizure but EEG was registered simultaneously.

2.2. Database and analysis

Data from individual cases were collected into one database. Duplicate cases were excluded. For each included case, the following variables were collected, if available: 1) regarding the patient history: sex, age at onset of epilepsy, age at onset of IP, therapy responsiveness; 2) regarding IP seizures: localization and lateralization of the seizure onset zone, ictal semiology, seizure propagation, seizure frequency and duration; 3) concerning the diagnostic work-up: interictal and ictal EEG, adequate neuroimaging, autoantibody testing for autoimmune encephalitis, etiology (based on histology or neuroimaging); 4) concerning therapy: antiepileptic drug therapy (AED), epilepsy surgery and outcome. We defined drug resistant epilepsy as proposed by the ILAE [6]. The diagnoses of LE and possible LE were based on the position paper on the clinical approach to diagnosis of autoimmune encephalitis by Graus et al. [7].

We had different levels of evidences regarding localization and lateralization, since there was no standard evaluating system applied to all patients. Values from 0 to 4 were assigned to each data to indicate the highest level of evidence: "0" if the diagnostic procedures were not mentioned at all, "1" if only interictal EEG results were mentioned, "2" if ictal scalp EEG data were presented without any data on neuroimaging, "3" if the presence of a relevant lesion on MRI was reported on; and "4" if the lesion was operated on in the course of epilepsy surgery with Engel Class I outcome; as used in our previous study [8].

In the course of our study, comparative analyses were also carried out. The alignments were based on sex, IP latency (patients in whom IP appeared at the onset of the epilepsy vs. those in whom it occurred later), and etiology.

Statistical analyses were performed using two-tailed binomial, Mann-Whitney, chi-square and Fisher exact tests. Data were analyzed with IBM SPSS Statistics 22. Results were considered to be statistically significant, if p-values were < 0.05.

3. Results

3.1. General characteristics

One hundred cases met the inclusion criteria (For individual reports see Supplement 1.). Since we also added 3 patients diagnosed and treated at the Department of Neurology, University of Pécs, 4 patients from the National Institute of Clinical Neurosciences, and 2 patients from the Department of Neurology, Odense University Hospital, 109 cases were included altogether. Data regarding sex were available in 105 cases: 72 of them were males. The mean age at onset of epilepsy was 39.5 ± 20.7 years (median: 39, IQR: 24–57), and the mean age at onset of IP appearance was 43.9 ± 17.8 years (median: 44, IQR: 29–58). Latency between the onset of epilepsy and IP was present in 5 cases (2–15 years). Data regarding seizure length was available in 39 cases, 10 of them were confirmed with EEG. Median seizure length was 30 s (min: 3; max: 240; IQR: 20–60). Regarding the analyzed variables, there was no difference between patients, in whom IP appeared at the beginning or after the epilepsy onset. In 67% of the patients, IP was preceded by an aura. It was accompanied by cold shiver in 53% and by other autonomic symptoms in 47%. Fifty-three percentages of the patients reported that IP never progressed into complex partial or generalized tonic-clonic seizures; 16% reported occasional, and 31% regular progression. Interictal and ictal EEG were normal in 23% and 5% of the patients, respectively. (See also Supplement 2)

Table 2
Data of patients with non-autoimmune or not established etiology.

Etiology	N
Not autoimmune origin	
Astrocytoma (9 grade III/IV, 5 grade II)	14
- 11 extended	
- 2 temporal	
- 1 unknown	
Developmental malformation	7
- 5 temporal	
- 1 frontal	
- 1 extended	
Posttraumatic lesion	4
- 3 temporal	
- 1 unknown	
Hippocampal sclerois/atrophy (MTLE)	4
Meningitis/encephalitis	2
- 2 temporal	
Other	8
- 5 temporal	
- 3 extended	
Not classified	
Normal MRI	20
Unknown lesion on MRI	2
- 1 extended	
- 1 temporal	
Hippocampal sclerois of unknown origin	12
Data regarding pathology was not available	13

MRI: magnetic resonance imaging; **MTLE**: mesial temporal lobe epilepsy;

3.2. Etiology

Etiology could be evaluated in 62 cases based on MRI and/or histological findings (Tables 1, 2). MRI was normal in 29% (Table 2). Among those patients in whom the MRI detected a pathological lesion, insular lobe involvement could be identified in 15%: 4 patients were diagnosed with astrocytoma, 1 with focal cortical dysplasia, 1 with vascular lesions and 1 patient had LE. In all of these cases the insular lesion further extended to the temporal, frontal, parietal lobes. Etiology did not show any accordance with neither the sex, nor the seizure frequency ($p = 1.000$, $p = 0.775$, respectively). Pilomotor seizures were longer in patients with LE ($p = 0.015$).

3.3. Sex differences, localization and lateralization

Neither IP in general, nor bilateral onset IP showed any lateralizing value ($p = 0{,}652$ and $p = 0{,}165$, respectively). Table 3 presents the results regarding the lateralizing value of ipsilateral IP. Ipsilateral IP showed lateralizing value only in males. IP was ipsilateral in 26 of the 28 male patients, and in 2 of the 7 female patients ($p < 0{,}001$ and $p = 0{,}453$, respectively). Pilomotor seizures showed a strong male dominance ($p < 0.001$). Seizure frequency was higher among females

Table 3
Lateralization and localization of the seizure onset zone.

Lateralization				
	HLOE	Result	Significance	N
Seizure onset zone	0	81% ipsilateral, 19% contralateral	$p < 0.001$	35
	1	81% ipsilateral, 19% contralateral	$p < 0.001$	35
	2	80% ipsilateral, 20% contralateral	$p = 0.001$	34
	3	87% ipsilateral, 13% contralateral	$p < 0.001$	30
	4	89% ipsilateral, 11% contralateral	$p = 0.039$	9
Localization				
	HLOE	Result	Significance	N
Seizure onset zone	0	92% temporal, 8% extratemporal	$p < 0.001$	90
	1	92% temporal, 8% extratemporal	$p < 0.001$	90
	2	92% temporal, 8% extratemporal	$p < 0.001$	90
	3	94% temporal, 6% extratemporal	$p < 0.001$	66
	4	86% temporal, 14% extratemporal	$p = 0.096$	14

HLOE: highest level of evidence; **N**: number of cases.

(median: 25/day, IQR: 3-60) than among males (median: 3/day, IQR: 1–11) ($p = 0.017$). Data on IP's seizure onset zone localizing value are displayed also in Table 3.

3.4. Therapy responsiveness

Pilomotor seizures were drug resistant in 68%. Epilepsy surgery was performed in 35 patients, and 16% of them continued to have IP despite of surgery.

4. Discussion

We performed a systematic review on cases of IP that allowed us to study this phenomenon in the highest number of subjects ever reported. Collecting data of > 100 patients enabled us to give a more comprehensive description of IP. We analyzed IP in relation to general characteristics, seizure semiology, sex differences, and also identified the most common etiologies that are of particular clinical importance.

IP resembles the physiological development of goosebumps induced by stress, cold and emotional stimuli. It is observed almost exclusively in adult onset epilepsies; there was only one report on a 3.5 year old child with ictal piloerection [9]. Our results correspond to those of Fogarasi et al. [10], who analyzed the autonomic changes in 514 seizures of 100 children with epilepsy (aged 10 months to 12 years), and could not identify ictal piloerection. In an experimental model by Mosuda et al. [11], piloerection in response to emotional stimuli increased with age. Therefore, it is likely that the autonomic nervous system has to reach a certain degree of maturation; otherwise epileptic activity is not able to cause IP. Another possible explanation would be an observational bias: children might be unable to adequately evaluate their seizure symptoms, failing to recognize IP. In our study, IP showed a clear male predominance, which was not attributed to the etiology. According to our knowledge, no sex specificity of piloerection was reported in the literature so far. In the healthy population, a generally higher sympathetic tone in males is a well-known phenomenon. In our previous study on ictal asystole associated with seizures, we found that the excessive ictal parasympathetic tone had a strong female predominance [8]. Moreover, we have also hypothesized a sex difference in seizure spread [12]. We hypothesize that the physiologically higher sympathetic tone and the tendency of a different seizure spread are the reasons that the male gender is more prone to generate sympathetic responses including piloerection during an epileptic seizure.

Regarding localization of the seizure onset zone, our results correspond to those of Loddenkemper et al. [3], who also observed temporal lobe dominance: 12 out of 14 patients had temporal lobe seizures. Based on stimulation experiments, several parts of the brain – especially structures of the limbic system – have been suggested as the symptomatogenic zone [3]. However, the role of the insula seems to be particularly plausible: this brain region has a well-known role in the central autonomic nervous system. In our cohort, 15% of the patients with abnormal MRI showed insular lobe involvement. Moreover, the ictal EEG did not show seizure activity in 5% of patients, suggesting the involvement of deep brain structures. We could not analyze the exact ictal seizure patterns in patients with abnormal EEG due to the lack of data, but Gillinder et al. [13] observed mid-temporal interictal and ictal patterns during IP. The authors argued that this pattern, atypical for mesial temporal lobe seizures, suggested insular lobe origin [13].

In comparison to Stefan et al. [4], who found left hemispheric dominance in IP, according to our results neither piloerection in general, nor bilateral onset piloerection were of any lateralizing value – corresponding to the analysis of Loddenkemper et al. [3]. Unilateral IP on the other hand, proved to be ipsilateral to the seizure onset zone. When the genders were analyzed separately, this association was only present in case of men. The reason for this difference between the two sexes may be attributed to the small sample size; however, sex differences in the function of the central autonomic nervous system have already been reported, including thermoregulation, heart-rate variance and pupillary reflexes [14–16]. Therefore, the different anatomy and/or function may indeed be responsible for such differences.

Although IP mostly remains to be a focal autonomic seizure without progression into complex partial or secondary generalized seizure, it is not a harmless condition. It is of special clinical interest, that the two most common underlying etiologies were glioma (mostly high grade gliomas) and autoimmune LE: these etiologies covered half of the cases, and one in four patients with IP had either glioma or autoimmune limbic encephalitis. Interestingly, LE with IP was associated with both well-characterized onconeural antibodies and antibodies against surface antigens indicating both T cell- and antibody-mediated pathogenic processes [7]. Antibodies against the voltage-gated potassium channel complex (VGKC) were particularly associated with IP, including antibodies against LGI1. It is possible that IP can be another seizure type in LGI1-encephalitis besides faciobrachial dystonic seizures (FBDS) [17,18] however, FBDS precedes encephalitis and is well-recognizable, while IP associated with epilepsy during encephalitis may miss attention. We also suggest that the reason for such particular association with LE and astrocytoma may be caused by the progressive nature of these diseases, i.e. significant changes develop in the brain in a relatively short period of time. However, the possibility of a selection bias can't be excluded completely: those cases of pilomotor seizures that are associated with autoimmune encephalitis - this newly discovered and intensively researched disease – might be reported more frequently. In our cohort with IP, 13 patients had active, definitive and 1 patient had possible LE [7]. There were 8 cases in the literature where the diagnosis of neither definite LE, nor probable LE could be established, however the authors suggested the seizure's autoimmune origin (Table 1).

When IP was the most prominent symptom, an average 5.2 year-long delay of the autoimmune encephalitis diagnosis was reported[5]. Moreover, Fisch et al. [19] reported a 68-year-old patient, in whom IP presented as the only symptom of glioblastoma multiforme. Considering the severity of LE and high-grade glioma, the 2 most common underlying pathologies of IP, extensive examination and close follow-up of these patients is of particular clinical importance.

5. Limitations

Due to the retrospective design of the study, there was no standard evaluating system applied to all patients, so we had different levels of evidences regarding localization and lateralization. Among the 29 cases, in which data were available on seizure length, only 10 cases were confirmed with EEG, so these should be interpreted cautiously.

6. Conclusion

IP is observed mainly in adult onset epilepsies, predominantly in males. The seizure onset zone is usually temporal. As for the symptomatogenic zone, the involvement of the insular lobe has been suggested, however this question needs further investigation. Besides faciobrachial dystonic seizures, characteristic in anti-Leucine-rich, glioma inactivated 1 (LGI1) encephalitis, pilomotor seizure seems to be also an etiology-specific seizure type: it is associated with autoimmune encephalitis and malignant brain tumor.

Disclosures of conflict of interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Funding

This work (JJ, BB, RH, SK, NK, DT) was supported by the Human Resources Development Operational Program (Grant No.: EFOP-362-16-2017-00008). Norbert Kovács was supported by the SNN125143 government-based grant. Dalma Tényi was supported by the ÚNKP-17-3New National Excellence Program of the Ministry of Human Capacities" and the Human Resources Development Operational Program (Grand No.: EFOP 3.6.1-16-2016-00004).

References

[1] Baumgartner C, Lurger S, Leutmezer F. Autonomic symptoms during epileptic seizures. Epileptic Disord 2001;3:103–16.
[2] Janszky J, Fogarasi A, Toth V, et al. Peri-ictal vegetative symptoms in temporal lobe epilepsy. Epilepsy Behav 2007;11:125–9.
[3] Loddenkemper T, Kellinghaus C, Gandjour, et al. Localising and lateralising value of ictal piloerection. J Neurol Neurosurg Psychiatry 2004;75:879–83.
[4] Stefan H, Pauli E, Kerling F, et al. Autonomic auras: left hemispheric predominance of epileptic generators of cold shivers and goose bumps? Epilepsia 2002;43:41–4.
[5] Rocamora R, Becerra JL, Fossas P, et al. Pilomotor seizures: an autonomic semiology of limbic encephalitis? Seizure 2014;23:670–3.
[6] Kwan P, Arzimanoglou A, Berg AT. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.
[7] Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391–404.
[8] Tényi D, Gyimesi C, Kupó P, et al. Ictal asystole: a systematic review. Epilepsia 2017;58:356–62.
[9] Seeck M, Zaim S, Chaves-Vischer V, et al. Ictal bradycardia in a young child with focal cortical dysplasia in the right insular cortex. Eur J Paediatr Neurol 2003;7:177–81.
[10] Fogarasi A, Janszky J, Tuxhorn I. Autonomic symptoms during childhood partial epileptic seizures. Epilepsia 2006;47:584–8.
[11] Masuda Y, Suzuki M, Akagawa Y, et al. Developmental and pharmacological features of mouse emotional piloerection. Exp Anim 1999;48:209–11.
[12] Janszky J, Schulz R, Janszky I, et al. Medial temporal lobe epilepsy: gender differences. J Neurol Neurosurg Psychiatry 2004;75:773–5.
[13] Gillinder L, Tjoa L, Mantzioris B. Refractory chronic epilepsy associated with neuronal auto-antibodies: could perisylvian semiology be a clue? Epileptic Disord 2017;19:439–49.
[14] Convertino VA. Gender differences in autonomic functions associated with blood pressure regulation. Am J Physiol 1998;275:1909–20.
[15] Kaciuba-Uscilko H, Grucza R. Gender differences in thermoregulation. Curr Opin Clin Nutr Metab Care 2001;4:533–6.
[16] Poynter WD. Pupil-size asymmetry is a physiologic trait related to gender, attentional function, and personality. Laterality 2017;22:654–70.
[17] Aurangzeb S, Symmonds M, Irani SR. LGI1-antibody encephalitis is characterised by frequent, multifocal clinical and subclinical seizures. Seizure 2017;50:14–7.
[18] Irani SR, Bien CG, Lang B. Autoimmune epilepsies. Curr Opin Neurol 2011;24:146–53.
[19] Fisch L, Mégevand P, Badoud A, et al. Pilomotor seizure: when paroxysmal gooseflesh heralds brain tumor. Neurology 2012;78:1189.