



## Case Report

# Successful surgical management of New Onset Refractory Status Epilepticus (NORSE) presenting with gelastic seizures in a 3 year old girl



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## ABSTRACT

Gelastic seizures (GS) are typically associated with hypothalamic hamartomas and present during childhood. However it is now known that GS can be found in focal epilepsies arising from other regions in the brain, including mesial and neocortical frontal, temporal and parietal regions.

GS have rarely been described as the presenting manifestation of New Onset Refractory Status Epilepticus (NORSE). In this article we describe a previously healthy 3-year-old who presented with an explosive onset of GS that were refractory to multiple anti-seizure medications. These seizures arose from the right frontal region. An extensive metabolic and immunological evaluation was negative. Her brain magnetic resonance imaging (MRI) was negative, however the Positron Emission Tomography (PET) scan showed a hypermetabolic region in the right frontal inferior gyrus.

She underwent a depth electrode evaluation that revealed a widespread irritative zone involving the PET "lesion" as well as mesial and neocortical regions in the right frontal lobe. The seizure onset zone was widespread and non-localizable. However the GS were associated with a clear ictal epileptiform discharge on invasive EEG arising from the depth of the superior frontal gyrus, which was not overlapping with the PET hypermetabolic region. She underwent a right frontal lobectomy sparing the primary motor region in the pre-central gyrus. She has remained seizure free for 15 months since. The pathological analysis showed focal cortical dysplasia type II in the region of the PET scan hypermetabolism. This case expands the clinical spectrum of GS to include cases of NORSE. Additionally the case highlights the role of resective surgery in GS presenting as NORSE and the potentially excellent outcome that can be achieved by early intervention.

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## 1. Introduction

Gelastic seizures classically are observed in epilepsy associated with hypothalamic hamartomas (HH) in the pediatric population. Although GS also occur in temporal and extra-temporal epilepsy without HH, this has been mostly reported in adults. Here we describe the case of a 3-year-old girl who presented with an explosive onset of GS that were entirely refractory to medical management. We detail the medical and surgical evaluations and treatment that were performed and describe the outcome.

## 2. Materials and methods

A 3 year old, right handed, bilingual (English and Spanish) girl presented with a sudden, new onset of paroxysmal spells of vocalization

described as laughter without a clear reason. She had no significant medical history and there were no preceding events prior to the onset, including febrile illnesses or unexplained fevers of any type. The patient did not have any known risk factors for epilepsy. She was the product of a normal pregnancy and birth and had no history of significant head trauma, episodes of meningitis or encephalitis, developmental delay in any domain or family history of epilepsy or seizures. The episodes increased in frequency dramatically from a few episodes per day to almost hourly episodes over a 3 day timespan. This increasing frequency was associated with the emergence of encephalopathy characterized by lethargy, slow speech and fatigue. She was admitted to the hospital and a video-electroencephalography (VEEG) demonstrated that the spells were seizures associated with epilepsy. The semiology of the seizures was gelastic/dacrystic with no clear associated mirth lasting 20–70 s. Additionally some of the seizures were associated with non-verse head and eyes deviation to the left.

The surface EEG revealed a stereotypical ictal and interictal patterns. The distribution of the interictal spike-and-wave complexes was restricted to the right frontal region at F8-F4 (Fig. 1). The ictal pattern

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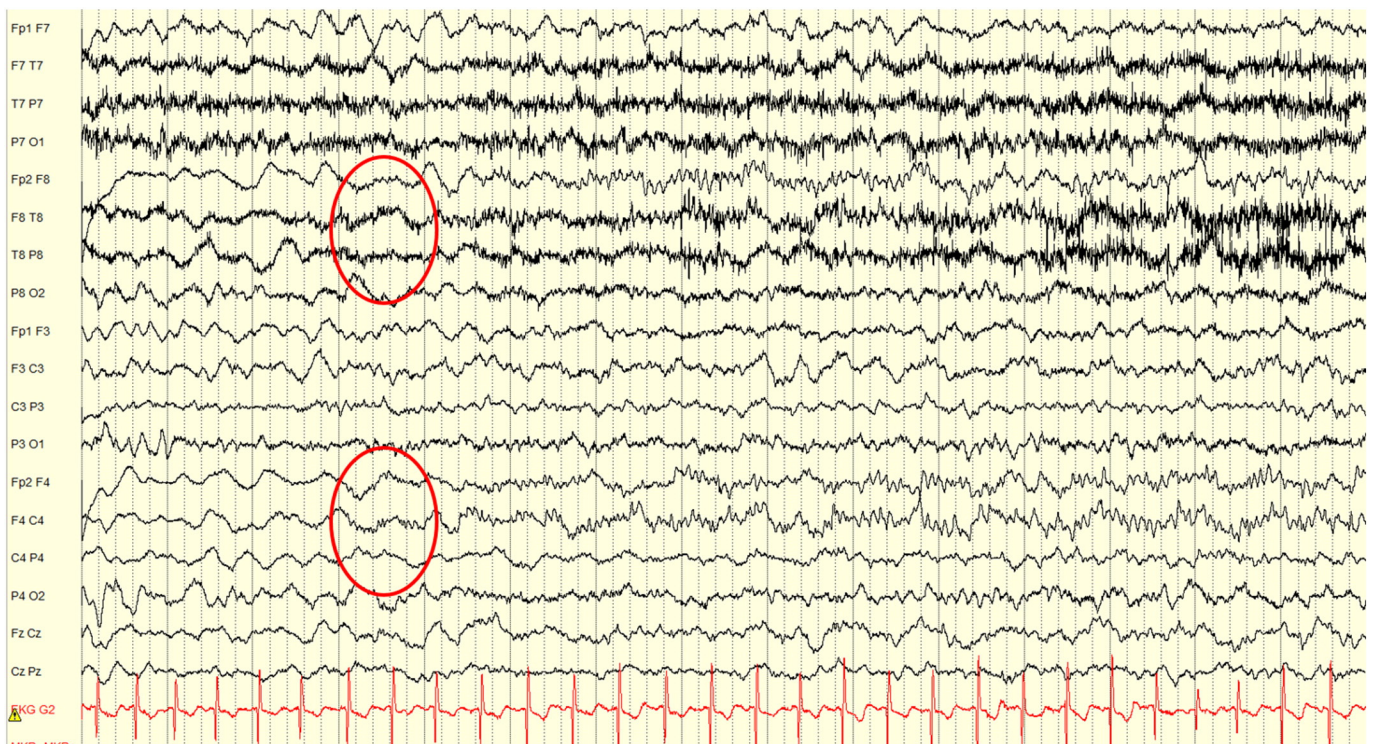
**Fig. 1.** Focal interictal epileptiform discharges with a maximum in the right frontal region F8-F4.

was composed of faster frequencies in the alpha range in the same distribution (F8-F4) with an initial spread to the rest of the right hemispheric regions followed by bilateral involvement (Fig. 2).

A brain MRI was normal without evidence of a hypothalamic hamartoma. The seizures proved resistant to multiple anti-seizure medications at high doses including levetiracetam, phenytoin, lorazepam, phenobarbital, topiramate, lacosamide, midazolam and pentobarbital

drips. Intravenous immune globulin IVIG and the Ketogenic diet were also ineffective. Despite these interventions, she continued to have seizures up to 5 seizures per hour.

Assessment of the patient’s cognitive functioning was attempted during the initial inpatient admission. Given the frequency of seizures, her engagement with testing was inconsistent. Parental report indicated prior normal development and average age-appropriate



**Fig. 2.** Seizure onset with fast frequencies in the alpha range. Same distribution as interictals, in the right frontal region F8-F4.

adaptive functioning. In contrast, her performance on testing indicated significantly impaired nonverbal and verbal skills at less than a 2 year age equivalency level interpreted as reflecting epileptic encephalopathy.

An extensive metabolic, infectious, paraneoplastic and autoimmune workup including a lumbar puncture and chest, abdomen, pelvis computed tomography (CT) were negative. A head PET scan showed hypermetabolic regions in the right inferior frontal gyrus and right thalamus (Fig. 3). Although the patient did not have a clinical seizure during the PET scan, the hypermetabolic region was consistent with the same localization as of the highly frequent interictal epileptiform discharges.

The surface EEG picture did not change in terms of localization of the interictal and ictal epileptiform patterns despite the multiple medications used and was always localized to the right frontal region with a maximum in the F8-F4 electrodes. The only period of time in which this EEG changed was when the patient was in burst-suppression using high dose pentobarbital infusion. After weaning off the pentobarbital, seizures returned with no changes in the semiology or localization of the EEG abnormalities. Magnetoencephalography (MEG) showed interictal dipoles in the right inferior frontal gyrus (Fig. 4). Due to the super-refractory status epilepticus and clear concordance in localization between the surface EEG, the PET scan hypermetabolic region and MEG dipoles, the patient underwent a stereotactic EEG (SEEG) evaluation. Ten depth electrodes were placed within the hypermetabolic PET lesion and in the surrounding frontal gyri, posterior, anterior, superior and inferior to the lesion, in a “cage” like approach, as well as the anterior insula, (Fig. 5).

### 3. Results

The SEEG study showed widespread interictal epileptiform discharges, reflecting a wide irritative zone in the contacts sampling the PET hypermetabolic region as well as multiple mesial and lateral contacts in the rest of the right frontal lobe (Fig. 6). There was no difference in the morphology of the interictals arising from the PET hypermetabolic region when compared to the rest of the interictals. The ictal pattern was composed of an initial increase in the frequency and amplitude of interictal discharges with a periodic component correlating to the patient either arousing from sleep or staring. (Fig. 7).

The gelastic part of the seizure occurred after the staring/arousal from sleep. It was associated with a focal discharge of paroxysmal fast with a frequency of 30–40 Hz restricted to contacts in the depth of the superior frontal gyrus (Fig. 8). The end of the ictal pattern showed a resurgence of the initial widespread ictal discharge (Fig. 9).

Based on the extent of the irritative and seizure onset zones, the patient underwent a motor sparing right frontal lobectomy. The pathology of the region corresponding to the PET hypermetabolic area

showed focal cortical dysplasia type IIA. The rest of the resected frontal lobe showed mild reactive gliosis. Seizures stopped immediately after the surgery. Her behavior after the resection initially was hyperactive and disinhibited. In marked contrast to her baseline behavior, she would bite and scratch others and had no understanding of the social limits. This improved tremendously after her medical regimen was simplified to phenobarbital monotherapy over the ensuing 6 months. Her mother then stopped phenobarbital against medical advice approximately 6 months after the resection. The patient has remained seizure free for 15 months following the surgery.

Repeat neuropsychological testing 8 months post-surgery reflected significant improvement in cognitive functioning. Although she evidenced some impairment on measures of attention, she was able to engage and respond to all tasks. Her performance otherwise indicated borderline general intellectual abilities. Notably, her nonverbal and visuospatial spatial skills, presumably controlled by the nondominant, typically right, hemisphere emerged as an area of relative strength.

### 4. Discussion

GS have been classically described in the context of lesional epilepsy with HH in the pediatric population [1]. It is now recognized that they are not pathognomonic of HH and can be found in temporal or extratemporal, lesional or non-lesional epilepsy, mostly in adults [2,3,4]. However there is a growing body of evidence of such cases in children [5,6].

The association of febrile illnesses of unknown origin with new or explosive onset refractory seizures or status epilepticus and encephalopathy in previously healthy children has been recognized for decades [7]. Prior to the onset of seizures, such patients are healthy with normal development and no risk factors for epilepsy. No identifiable etiology of seizures is found. The majority of these patients develop a prolonged course of drug-resistant seizures, prominent cognitive delays and poor long term outcomes [8]. Different names have been proposed to describe these cases; the most common of which is fever induced refractory epileptic encephalopathy in school age children (FIRES) [9,10] and NORSE [11]. Although the presence of a preceding febrile illness has been described in NORSE patients, it is not an essential criterion for the diagnosis of NORSE [11,12]. Furthermore, NORSE has been described almost exclusively in adult patients [12]. The semiology of seizures presenting as NORSE is diverse and includes clinical and subclinical seizures of different types. About half of NORSE cases have an unknown etiology and the other half have variable causes but mostly autoimmune or paraneoplastic etiologies. The prognosis of NORSE is generally poor with epilepsy developing in most cases [12]. The explosive onset of seizures without a preceding febrile illness and the lack of any autoimmune or paraneoplastic etiology in the patient

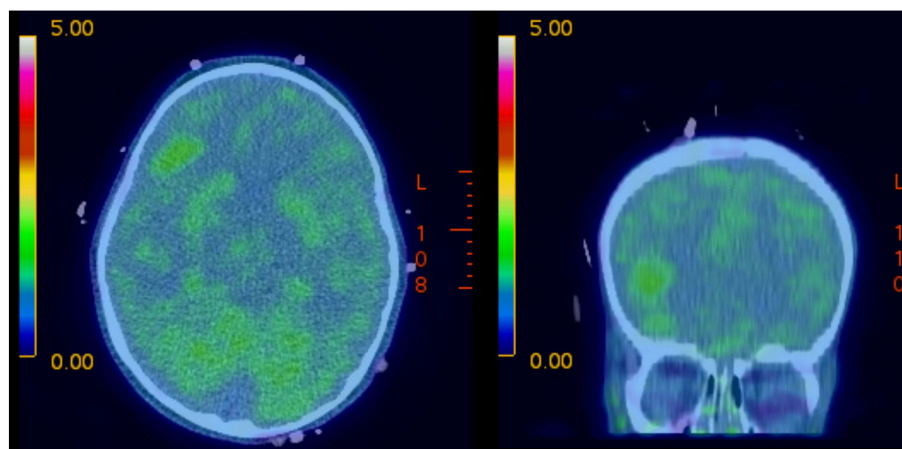
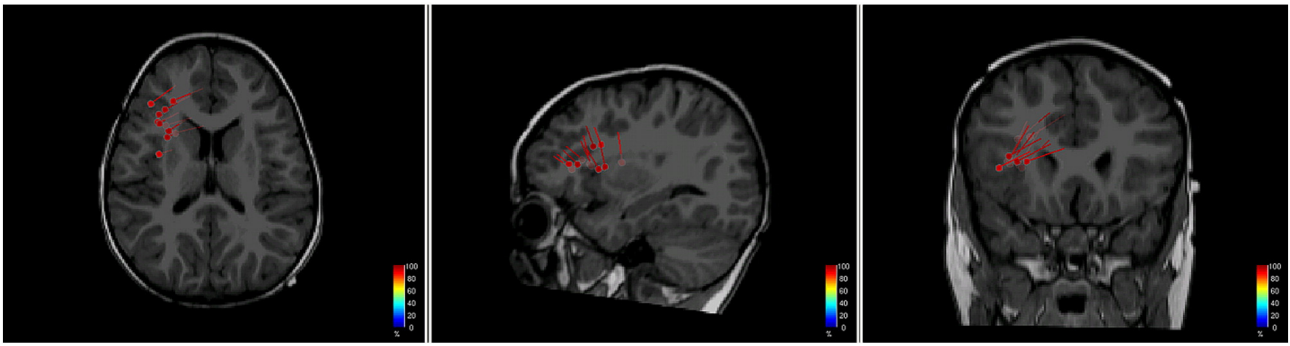


Fig. 3. Increased radio-pharmaceutical uptake in the anterior aspect of the right inferior frontal gyrus.



**Fig. 4.** MEG interictal spike clusters in the inferior and middle frontal gyri.

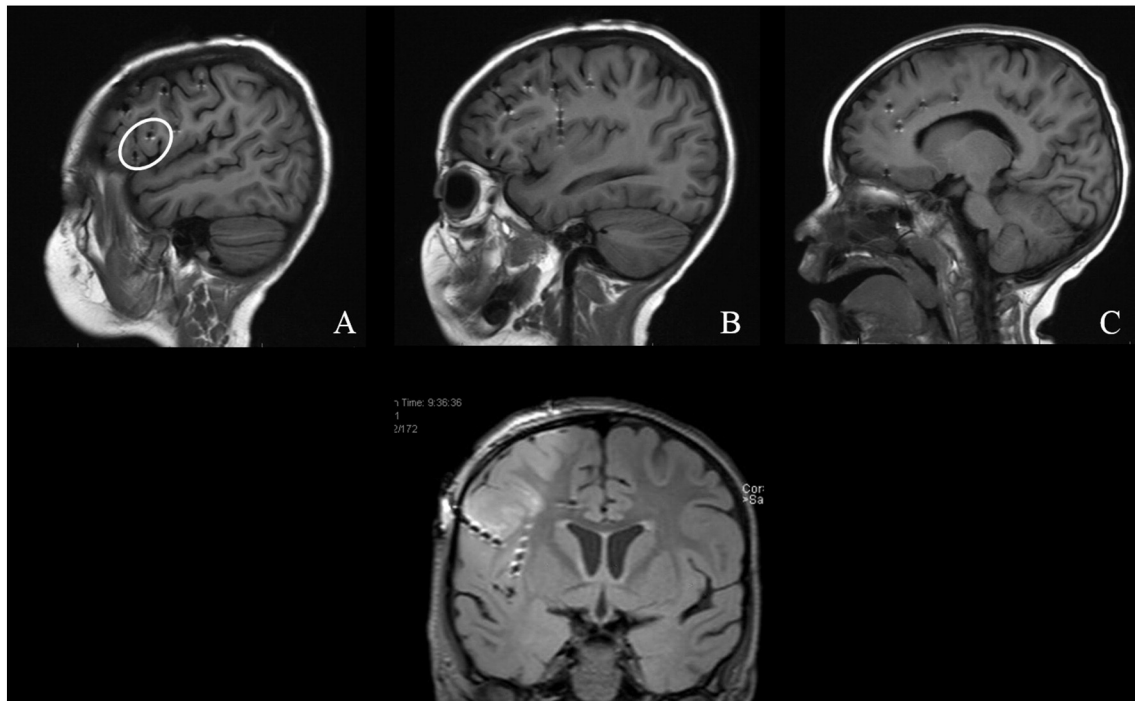
described here are typical features of NORSE. This contrasts to FIRES for which the presence of a febrile illness of an unknown origin is essential for the diagnosis. This case also highlights that NORSE can occur in pediatric patients, as young as 3 years of age.

The pathophysiology underlying the production of GS is not entirely understood. Based on few stimulation studies, it was proposed that the anterior cingulate region is involved in the motor act of laughter, while the basal temporal cortex is involved in processing of laughter’s emotional content in humans [13,14]. In this patient, the gelastic component of her seizures occurred when the ictal discharge evolved in the contacts placed in deeper parts of the superior frontal gyrus. This supports the theory that the functional network involved in the production of gelastic seizures extends beyond the cingulate gyrus and involves the superior frontal gyrus as previously reported [15].

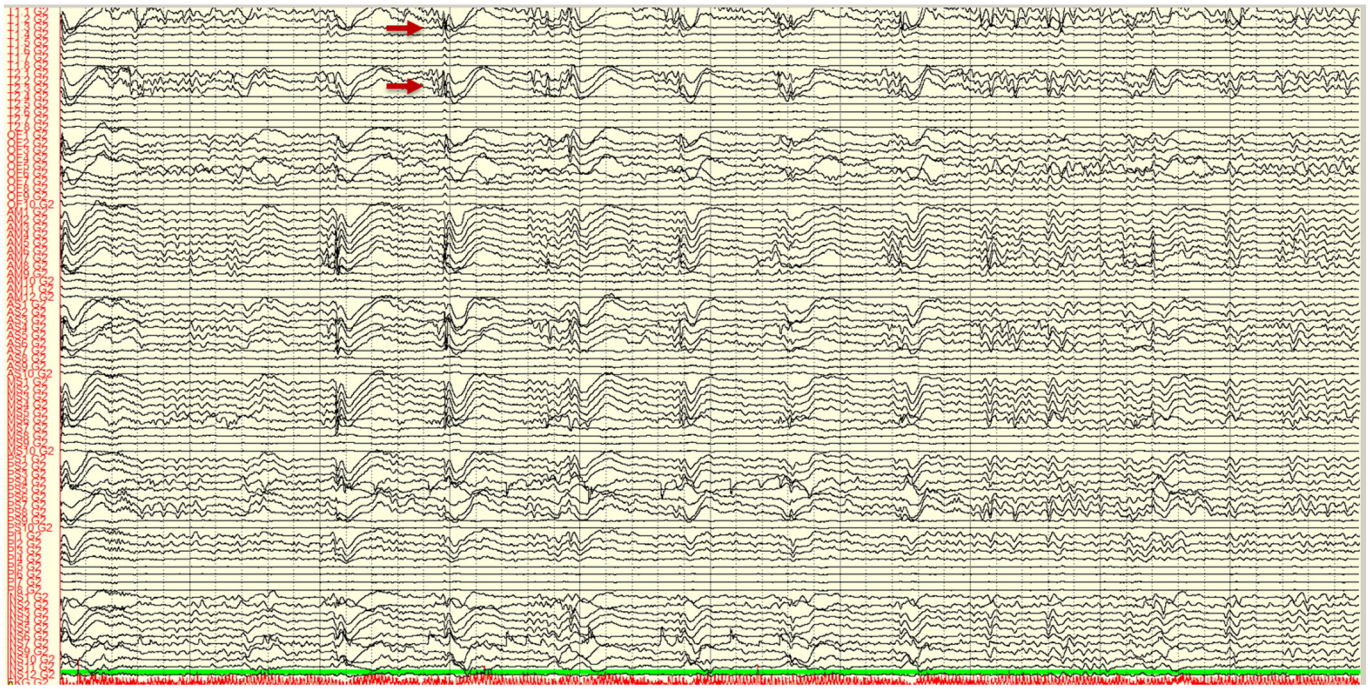
Given the refractory nature of seizures in the context of NORSE to high-dose suppressive therapy [16], other modalities of therapy have been used in this setting. Nabbout reported on 7 patients with FIRES who were treated with the ketogenic diet after failing multiple anti-seizure medications. These patients showed focal interictal and ictal EEG involving the temporal regions on both sides alternatively. All patients responded to the diet initially with one patient experiencing

recurrence of the refractory status and dying in the setting of discontinuing the diet. The other six patients responded favorably with resolution of the refractory status RSE. However all of them experienced recurrent, isolated, shorter seizures within 1–6 months from the onset despite continuing the diet for 6–24 months [17]. Appavu reported a case series of 10 patients with super refractory status epilepticus unresponsive to anesthetic medications that were treated with the ketogenic diet. Of those, one patient had NORSE and one patient had FIRES. Both patients had generalized refractory status epilepticus on EEG. The ketogenic diet was effective in the FIRES case with subsequent weaning off the anesthetic medications and resolution of the refractory status but this continued to have daily seizures after discharge from the hospital despite further treatment with anti-seizure medications. The patient with NORSE did not respond to the diet and died in hospice [18].

Kenny-Jung reported on a 32 month old patient presenting with FIRES. She had migrating, frequent repetitive, multifocal clinical and subclinical seizures arising independently from both hemispheres failing multiple anti-seizure medications and the ketogenic diet. She was treated with Anakinra, a recombinant version of the human interleukin 1 (IL-1) receptor antagonist, the selective endogenous



**Fig. 5.** Location of SEEG placement, covering the PET hypermetabolic region and the areas surrounding it. The sagittal cuts show the trajectory of the orthogonal electrodes from lateral (A) to mesial (C) aspects. The circle in (A) shows the 2 electrodes sampling the region corresponding to the hypermetabolic area found on PET. There is one superior to inferior depth electrode covering the mesial part of the anterior insula as shown in (D).



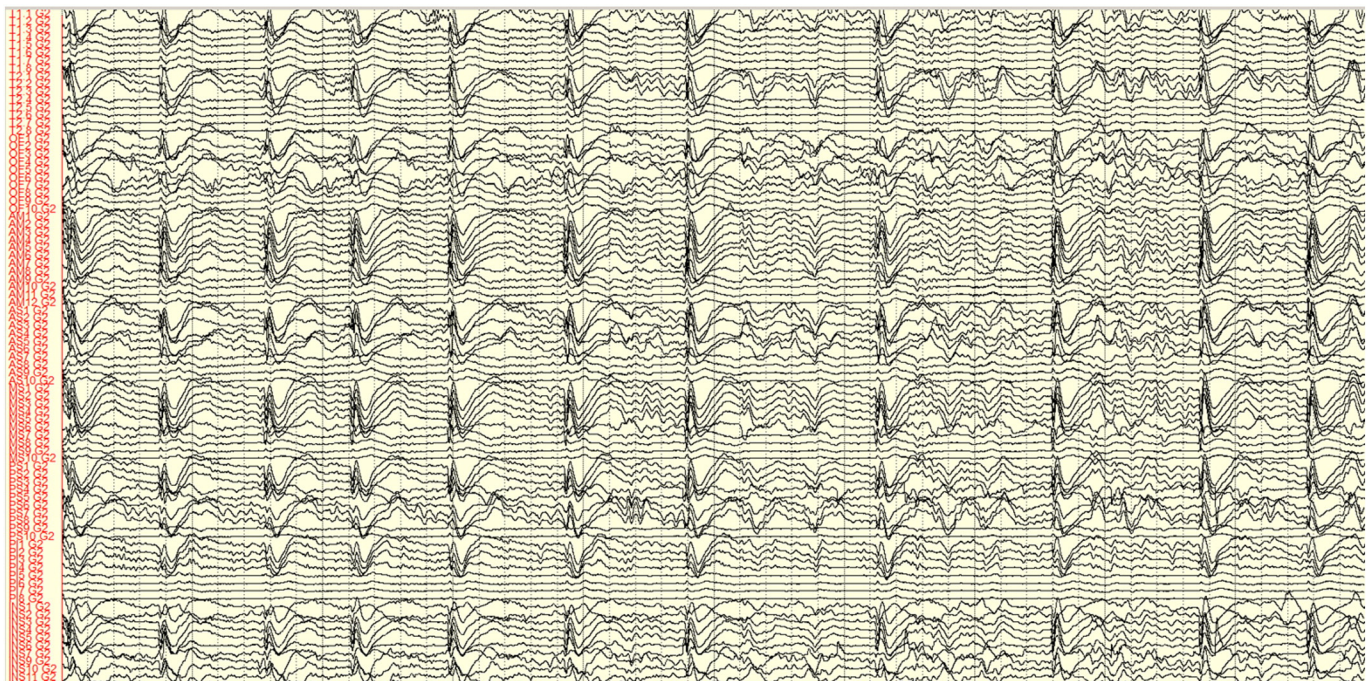
**Fig. 6.** SEEG interictal sample. The arrows show the contacts within the hypermetabolic region on PET. The distribution of the interictals is widespread including contacts in the mesial and lateral frontal regions. The morphology of the interictals is the same in all contacts.

antagonist of the IL-1 receptor type 1 (IL-1R1), which inhibits the biological actions of IL-1 $\beta$ . Anakinra was used on two separate occasions, days 6–23 and then days 54 onwards of the refractory status. The patient responded well during the second trial and remained on Anakinra after discharge from the hospital. However she continued to have rare isolated focal clinical seizures on treatment with Anakinra, felbamate, and levetiracetam [19].

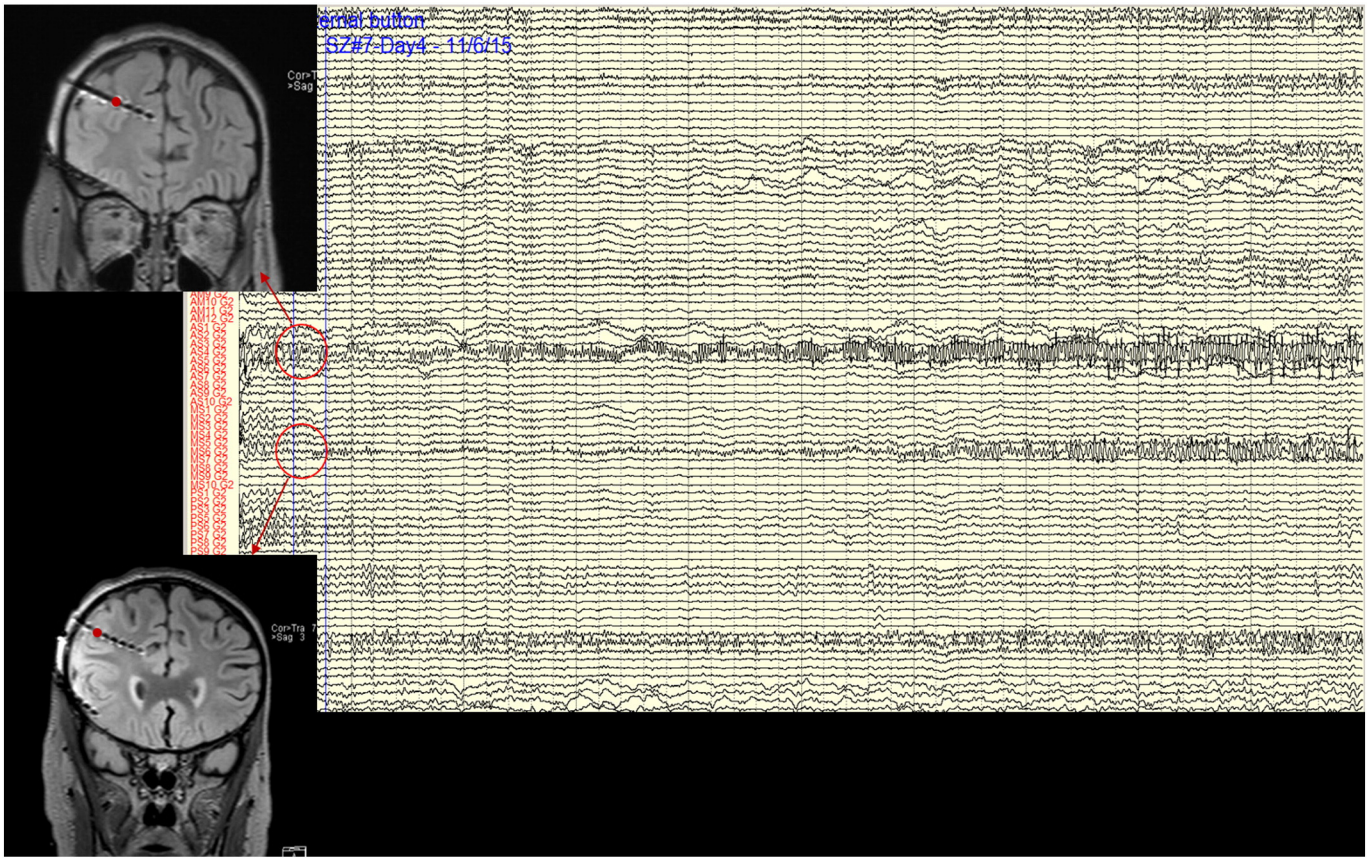
The presence of refractory status epilepticus with or without previously diagnosed symptomatic/lesional focal epilepsy has been reported

to be successfully treated with resective epilepsy surgery in adults and children in small case series and case reports [20,21,22,23,24,25].

Alexopoulos described 10 patients with a previous diagnosis of epilepsy who presented with status epilepticus that was refractory to aggressive medical therapy >2 weeks in the pediatric intensive care unit. The age of onset of status ranged from 3 day to 16 years. Nine of those patients had lesional MRI with malformation of cortical development, hemimegalencephaly, perinatal stroke or Rasmussen's syndrome. One patient had an unclear diagnosis thought to have been



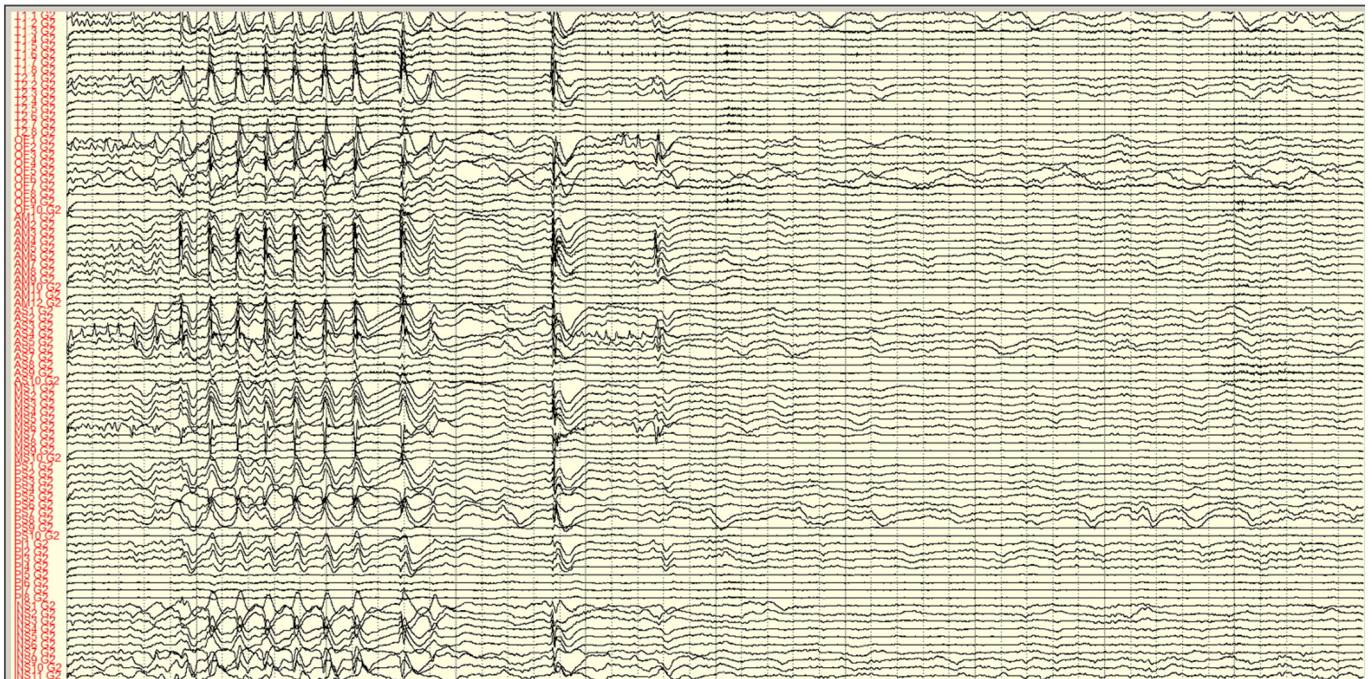
**Fig. 7.** Seizure onset on SEEG. The morphology and distribution of the ictal pattern is similar to the interictal discharges. However there is a clear increase in amplitude and frequency showing an ictal evolution. This SEEG picture correlated to the patient staring or waking up from sleep.



**Fig. 8.** The location of the contacts associated with the gelastic/dacrystic part of the seizure marked by the red circles on EEG and red dots on MRI. The EEG seizure onset occurs prior to the symptomatic onset of laughter and is more widespread, mirroring that of the irritative zone. (For interpretation of the references to color in this figure legend, the reader is referred to the online version of this chapter.)

Rasmussen encephalitis. MRI and EEG abnormalities were congruent during refractory status in 8 of 10 patients and incongruent in 2 of 10 (one had hemispheric encephalomalacia opposite the side with ictal

and interictal epileptiform abnormalities, whereas the other had diffuse bilateral cerebral volume loss and exclusively unihemispheric EEG abnormalities). No invasive EEG evaluations were done due to the



**Fig. 9.** The end of the ictal pattern. After the focal paroxysmal fast activity, correlating with the gelastic component of the seizure, there is a recurrence of the same widespread ictal pattern at the onset of seizures before the ictal pattern has ended.

presence of clear abnormalities on the MRI. Surgeries included functional hemispherectomy in 6/10, frontal resection in 2/10, frontoparietal resection in 1/10 and temporo-parietal-occipital resection in 1/10. Refractory status stopped acutely in all 10 patients. At post-operative follow-up, ranging from 4 months to 6.5 years, 7 patients (70%) remained seizure free and 2 (20%) had significant improvement in their epilepsy compared with the preoperative state. In 1 patient epilepsy remained unchanged [16].

Functional imaging modalities such as PET and ictal single-photon emission computed tomography (SPECT) have been used in the critically ill patients with refractory status to further help the resective surgical planning. Bhatia et al. described a series of 15 pediatric patients with a previous diagnosis of epilepsy presenting with refractory status between 4 months and 19 years of age. All patients had focal or lateralized seizures. Seven patients had malformations of cortical development, including focal cortical dysplasia or hemimegalencephaly. Six patients had nonspecific changes, including atrophy (diffuse or focal perirolandic), hippocampal signal change, or periventricular leukomalacia. Two patients had normal MRIs. SPECT scans were done in 12 patients, and localized hyperperfusion was seen in 10. Three patients received PET scans, 2 patients had focal hypometabolism, and 1 showed focal hypermetabolism suggesting a localized ictal onset. Twelve patients with abnormal MRIs underwent intraoperative electrocorticography (ECoG). Three patients (including the patients with normal MRIs) received extraoperative monitoring. Grids and strips were utilized in all patients. The initial resection included corticectomy in 13 patients, following failed multiple subpial transections in 1 patient, and 6/13 patients had complete lobectomy. The remaining 7 patients underwent limited corticectomy. One patient underwent hemispherectomy for hemimegalencephaly and one patient multiple subpial transections only.

Refractory status resolved in 14 patients after the initial resection. One patient received a limited initial frontal cortical resection that was followed by complete frontal lobectomy and multiple subpial transections in the Broca's region and refractory status was also controlled. Four patients continued to have frequent intermittent seizures and required additional surgical intervention after the initial corticectomy (lobar resection in 2 and hemispherectomy in 2 patients). Final outcome was seizure freedom (Engel Class I) in 7 patients, 90% seizure reduction (Engel Class II) in 4 patients, and persistent seizures in 4 patients (Engel Class III or IV). The authors concluded that SPECT is especially useful as it guided the invasive monitoring and surgical resections in 10/12 patients [26].

MEG is increasingly utilized in presurgical planning for resective epilepsy surgery. Mohamed reported 5 pediatric patients (age range 2.5–14 years) with established epilepsy who failed medical therapy in the setting of refractory status. Three had abnormal MRIs showing cortical dysplasia, 1 had a normal MRI and 1 patient had an initial normal MRI that later showed diffusion restriction in the right hippocampus associated with increased signal intensity on T2 and FLAIR sequences. In all five patients, interictal discharges were widespread. Ictal-onset EEG findings were localized to one region in three patients and two regions in the same hemisphere the other two patients. Interictal MEG revealed unilateral clustered MEG spike sources in four patients and bilateral in one. Ictal MEG were obtained in 2 patients, both of which had ictal MEG clusters within the interictal MEG clusters and those were congruent with the ictal surface EEG recordings. MEG data was used to plan the subdural grids placement in 4 patient, one of which had extraoperative monitoring. Limited cortical excisions were done in 2 patients, hemispherectomy in 1 and anterior temporal lobectomy 2 patients. The resections included the areas showing the MEG clusters in 4 patients, all of which had resolution of refractory status and 2 became seizure free (one had a hemispherectomy). The authors concluded that complete resection of clustered MEG spikes can control refractory status and possibly lead to a seizure free outcome [27].

Basha et al. reported on a surgical cohort of 9 adult patients (20–68 years) who presented with refractory status and failed intravenous anesthetic medications alongside conventional anti-seizure medications. Five patients had de novo status and 4 had a previous diagnosis of epilepsy. EEGs showed focal and multifocal seizures. Eight patients had abnormal MRIs. Five patients had focal or diffuse nonspecific hyperintense lesions on T2-weighted images. One patient had an intraparenchymal hemorrhage, one a resection cavity with focal enhancement and one mesial temporal sclerosis with unilateral hippocampal atrophy. Only one patient had a normal MRI. The etiology was defined in all patients except the one who had a normal MRI. One patient underwent extraoperative (ECoG) recording and the other 8 patient had intraoperative ECoG, all using subdural grids and strips. Seizures were captured in 4 patients. Eight patients had unilobar resections while 2 underwent multilobar resections. Refractory status resolved immediately in 6 patients, 2 patients had persistent refractory status and 1 patient died [28].

Few case reports exist describing resective surgery for focal epilepsy with apparently asymptomatic/non-lesional refractory status [29]. Desbiens reported 4 patients with a previous diagnosis of epilepsy who developed life threatening refractory focal status leading to intubation in 3 patients. All those patients had normal 1.5 Tesla MRIs. The EEG was focal showing seizures arising from the central region in 2, frontocentral region in 1 and midfrontal region in 1 patient. Intraoperative ECoG was done in 3 patients confirming the focal onset of seizures. Two patients had corticectomies in the central and 1 in the frontal regions. One underwent an en bloc resection of the central area after two unsuccessful corticectomies and cortical transection. Two patients became seizure free and 2 had good control of seizures. Pathology revealed malformation of cortical development in all patients [30].

Ng described a case of a 4 year old girl with cryptogenic epilepsy since the age of 1 year. She presented with focal refractory status with a focal EEG showing abnormalities at P4. An MRI was normal. She initially underwent multiple subpial transections that did not control the refractory status. Subsequently an invasive evaluation using grids and strips led to a tailored resection of the mesial parietal region and she was weaned off successfully off all anti-seizure medications in 1 year. The pathology showed focal cortical dysplasia [31].

SEEG has been reported to be used in evaluating a patient with refractory status previously. Oderiz reported an 8-year-old with epilepsy starting at age 7, who presented with focal refractory status and MRI showing right hemispheric atrophy. The EEG showed spikes arising from the right anterior temporal region. Twelve SEEG depth electrodes used to cover the right fronto-temporal region showed the seizure onset zone to be the right amygdala and hippocampus. A right anterior temporal lobectomy was planned, however the amygdala and hippocampus were not resected because of bleeding and congestive edema in the lesion area. Refractory status resolved after surgery and she attained long term seizure freedom over 4 years [32].

The decision to proceed with a surgical evaluation in our patient was made due to the super-refractory nature of the epilepsy, including the failure to produce any reasonable control of the seizures despite prolonged treatment with high doses of intravenous anti-seizure and anesthetic agents. The gelastic semiology and focal EEG interictal and ictal patterns in the right frontal region remained unchanged despite multiple changes in the medical regimen over the course of 6 weeks. We believed that this stability reflected a localized epileptogenic zone related to an occult focal cortical dysplasia based on the frequent and persistent spiking on surface EEG. The finding of a hypermetabolic region on PET that was congruent with the location of the interictal and ictal EEG and the MEG clusters further supported our hypothesis. The decision to proceed with an SEEG evaluation was made in order to tailor a limited cortical resection if possible. Despite the very focal paroxysmal fast activity in the depth of the superior frontal gyrus that accompanied the gelastic component of the seizures, the ictal onset

**Table 1**  
Review of the literature of pediatric case series of refractory status epilepticus treated surgically.

Study	Patient number/age of surgery	MRI	Surgery	Outcome
Alexopoulos [16]	10 (3 days-16 years)	3 Malformation of cortical development 3 Hemimegalencephaly 1 Perinatal stroke 1 Tuberos Sclerosis 1 Rasmussen encephalitis 1 Unknown	3 Functional hemispherectomy 3 Anatomical hemispherectomy 4 Lobectomy/focal cortical resection	7 Seizure free 2 Seizures improved 1 Seizures unchanged
Bhatia [26]	15 (4 months-19 years)	6 Malformation of cortical development 3 Atrophy 2 Hippocampal abnormalities 1 Hemimegalencephaly 1 Hydrocephalus 2 Normal	13 Lobectomy/focal cortical resection 2 Hemispherectomy	8 Seizure free 5 (50–90%) improvement 2 (<50%) improvement
Mohamed [27]	5 (2.5–14 years)	3 Malformation of cortical development 2 Increased signal due to SE	4 Lobectomy/focal cortical resection 1 Hemispherectomy	2 Seizure free 3 Residual seizures
Desbines [30]	4 (4–21 years)	4 Normal	4 Lobectomy/focal cortical resection	2 Seizure free 1 Single post-operative seizure 1 Seizures improved
Ng [31]	1 (4 years)	1 Normal	1 Focal cortical resection	1 Seizure free
Oderiz [32]	1 (4 years)	1 Right hemispheric atrophy	1 Lobectomy	1 Seizure free
Dubey [33]	1 (6 years)	1 Malformation of cortical development	1 Focal cortical resection	1 Seizure free

was clearly not limited to the same region and involved both mesial and lateral contacts in the frontal lobe. This argued against performing a limited cortical resection and the conclusion was that a generous frontal lobectomy will have a higher chance of producing good seizure control. Our suspicion of occult focal cortical dysplasia was confirmed with the pathology showing type IIA cortical dysplasia in the area corresponding to the PET hypermetabolic region.

This case represents several unique features that are described for the first time in the literature. From a semiological standpoint, the absence of a previous history of epilepsy, absence of a preceding fever and a NORSE-like onset of gelastic seizures at this young age has not been reported previously. The youngest patient reported to have a similar presentation was 6 years at the time of NORSE [33]. That patient also required a surgical resection following failure of multiple medications and surgery was successful in producing excellent, long term seizure control. From a management perspective, this case illustrates that SEEG can be utilized acutely in cases of refractory status. In general SEEG is better tolerated with less pain and avoids the need to perform a craniotomy which may place less burden on such critically ill patients. Additionally SEEG provides the possibility of sampling deeper regions of the brain when compared to grids or strips. In this case SEEG allowed us to sample the PET hypermetabolic region and other mesial frontal structures.

The timing of performing an invasive evaluation resective surgery in critically ill patients with refractory status remains poorly understood [28,34]. The rarity of such cases makes large population studies impossible and subsequently limits the quality of data and the certainty of conclusions. The extensive workup that is usually obtained in these cases, typically including metabolic, genetic and autoimmune testing, may require days or sometimes weeks to complete and thus may delay the surgical option. Additionally variable etiologies can cause refractory status and this is likely to have a role in the success rate with resective surgeries across different etiologies, including NORSE patients.

Although EEG and MRI are the mainstay testing methods used in the presurgical evaluation for those patients, additional neurophysiological and functional imaging modalities have been successfully utilized in this setting and can be considered when available including PET, SPECT and MEG. The presence of focal refractory status with congruent findings on different tests should always prompt the treating physicians to consider resective surgery as an option. This applies to both, lesional and non-lesional MRI cases. Invasive monitoring in this cohort of patient with subdural grids and strips or SEEG can and should be used when needed to further help with the surgical planning. Despite the limitations,

available literature suggests that such surgeries can have a high success rate in terminating refractory status of various etiologies. (See Table 1.)

## 5. Conclusion

To our knowledge this is the youngest patient presenting with GS as NORSE who underwent resective epilepsy surgery with subsequent seizure freedom.

Our case highlights that GS can have an explosive onset as part of NORSE, which in the absence of HH, should prompt an extensive workup to rule out any treatable infectious, immunological or paraneoplastic causes.

The failure of aggressive medical therapy delete HDST in controlling seizures in NORSE should prompt a surgical workup with MRI, PET, SPECT and MEG when applicable. The absence of lesions on MRI should not be considered a contraindication to epilepsy surgery, especially if PET abnormalities are identified which are concordant with the other electrophysiological testing. Resective surgery can have a high success rate with excellent seizure outcome if the irritative and ictal onset zones are adequately sampled and a resection is feasible.

## Disclosure

All authors involved in this study have contributed equally in caring for the patient, collecting data and writing the manuscript. To the best of our knowledge, no conflict of interest, financial or other, exists. No honorarium or grant was given to produce the manuscript.

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## References

- [1] Harvey AS. Hypothalamic hamartomas. In: Lüders HO, editor. *Textbook of epilepsy surgery*. London: Informa Healthcare; 2007. p. 354–61.
- [2] Gutierrez C, Asadi-Pooya AA, Skidmore CT, Tobochnik SD, LoPinto-Khoury C, Sperling MR. Clinical features and postoperative seizure outcome in patients with drug-resistant gelastic seizures without hypothalamic hamartoma. *Epilepsy Behav* Nov 2016;64(Pt A):90–3.
- [3] Tran TP, Truong VT, Wilk M, Tayah T, Bouthillier A, Mohamed I, et al. Different localizations underlying cortical gelastic epilepsy: Case series and review of literature. *Epilepsy Behav* Jun 2014;35:34–41.



- [4] Kovac S, Diehl B, Wehner T, Fois C, Toms N, Walker MC, et al. Gelastic seizures: Incidence, clinical and EEG features in adult patients undergoing video-EEG telemetry. *Epilepsia* Jan 2015;56(1):e1–5.
- [5] Uribe-San-Martin R, Ciampi E, Lawson-Peralta, Acevedo-Gallinato K, Torrealba-Marchant G, Campos-Puebla M, et al. Gelastic epilepsy: Beyond hypothalamic hamartomas. *Epilepsy Behav Case Rep* Aug 2015;16(4):70–3.
- [6] Savasta S, Budetta M, Sparta MV, Carpentieri ML, Trasimeni G, Zavras N, et al. Gelastic epilepsy without hypothalamic hamartoma: Three additional cases. *Epilepsy Behav* Aug 2014;37:87–90.
- [7] Lyon G, Dodge PR, Adams RD. The acute encephalopathies of obscure origin in infants and children. *Brain* Dec 1961;84:680–708.
- [8] Ismail FY, Kossoff EH, AERRPS, DESC, NORSE, FIRES: multi-labeling or distinct epileptic entities? *Epilepsia* Nov 2011;52(11):e185–9.
- [9] van Baalen A, Häusler M, Boor R, Rohr A, Sperner J, Kurlemann G, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalopathy in childhood. *Epilepsia* Jul 2010;51(7):1323–8.
- [10] Nabbut R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation-mediated status epilepticus. *Lancet Neurol* Jan 2011;10(1):99–108.
- [11] Wilder-Smith EP, Lim EC, Teoh HL, Sharma VK, Tan JJ, Chan BP, et al. The NORSE (New-onset Refractory Status Epilepticus) syndrome: defining a disease entity. *Ann Acad Med Singapore* Aug 2005;34(7):417–20.
- [12] Gaspard N, Foreman B, Alvarez V, Cabrera Kang C, Probasco JC, Meyers E, et al. New-onset refractory status epilepticus. Etiology, clinical features and outcome. *Neurology* Nov 3, 2015;85(18):1604–13.
- [13] Arroyo S, Lesser RP, Gordon B, Uematsu S, Hart J, Schwerdt P, et al. Mirth, laughter and gelastic seizures. *Brain* Aug 1993;116:757–80.
- [14] Oehl B, Biethahn S, Schulz-Bonhage A. Mirthful gelastic seizures with ictal involvement of temporobasal regions. *Epileptic Disord* Mar 2009;11:82–6.
- [15] Unnwongse K, Wehner T, Bingaman W, Foldvary-Schaefer N. Gelastic seizures and the anteromesial frontal lobe: a case report and review of intracranial EEG recording and electrocortical stimulation case studies. *Epilepsia* Oct 2010;51:2195–8.
- [16] Alexopoulos A, Lachhwani D, Gupta A, Kotagal P, Harrison AM, Bingaman W, et al. Resective surgery to treat refractory status epilepticus in children with focal epileptogen-esis. *Neurology* Feb 8, 2005;64(3):567–70.
- [17] Nabbut R, Mazzuca M, Hubert P, Peudennier S, Allaire C, Flurin V, et al. Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES). *Epilepsia* Oct 2010;51(10):2033–7.
- [18] Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. *Seizure* Oct 2016;41:62–5.
- [19] Kenney-Jung DL, Vezzani A, Kahoud RJ, LaFrance-Corey RG, Ho ML, Muskardin TW, et al. Febrile infection-related epilepsy syndrome treated with Anakinra. *Ann Neurol* Dec 2016;80(6):939–45.
- [20] Ma X, Liporace J, O'Connor MJ, Sperling MR. Neurosurgical treatment of medically intractable status epilepticus. *Epilepsy Res* Jul 2001;46(1):33–8.
- [21] Duane DC, Ng YT, ReKate HL, Chung S, Bodensteiner JB, Kerrigan JF. Treatment of refractory status epilepticus with hemispherectomy. *Epilepsia* 2004;45(8):1001–4.
- [22] Barros P, Brito H, Ferreira PC, Ramalheira J, Lopes J, Rangel R, et al. Resective surgery in the treatment of super-refractory partial status epilepticus secondary to NMDAR antibody encephalitis. *Eur J Paediatr Neurol* May 2014;18(3):449–52.
- [23] Krsek P, Tichý M, Belsan T, Zámecník J, Paulas L, Faladová L, et al. Life-saving epilepsy surgery for status epilepticus caused by cortical dysplasia. *Epileptic Disord* Sep 2002;4(3):203–8.
- [24] Weimer T, Boling W, Palade A. Neurosurgical therapy for central area status epilepticus. *W V Med J* Sep-Oct 2012;108(5):20–3.
- [25] Schrader DV, Steinbok P, Connolly M. Urgent, resective surgery for medically refractory, convulsive status epilepticus. *Eur J Paediatr Neurol* Jan 2009;13(1):10–7.
- [26] Bhatia S, Ahmad F, Miller I, Ragheb J, Morrison G, Jayakar P, et al. Surgical treatment of refractory status epilepticus in children: clinical article. *J Neurosurg Pediatr* Oct 2013;12(4):360–6.
- [27] Mohamed IS, Otsubo H, Donner E, Ochi A, Sharma R, Drake J, et al. Magnetoencephalography for surgical treatment of refractory status epilepticus. *Acta Neurol Scand* Apr 2007;115(4 Suppl):29–36.
- [28] Basha MM, Suchdev K, Dhakar M, Kupsky WJ, Mittal S, Shah AK. Acute resective surgery for the treatment of refractory status epilepticus. *Neurocrit Care* Mar 29, 2017. <http://dx.doi.org/10.1007/s12028-017-0381-z> [Epub ahead of print].
- [29] Costello DJ, Simon MV, Eskandar EN, Frosch MP, Henninger HL, Chiappa KH, et al. Efficacy of surgical treatment of de novo, adult-onset, cryptogenic, refractory focal status epilepticus. *Arch Neurol* 2006;63(6):895–901.
- [30] Desbiens R, Berkovic SF, Dubeau F, Andermann F, Laxer KD, et al. Life-threatening focal status epilepticus due to occult cortical dysplasia. *Arch Neurol* Jul 1993;50(7):695–700.
- [31] Ng YT, Kim HL, Wheless JW. Successful neurosurgical treatment of childhood complex partial status epilepticus with focal resection. *Epilepsia* Mar 2003;44(3):468–71.
- [32] Oderiz CC, Aberastury M, Besocke AG, Sinner J, Comas-Guerrero B, Ciraolo CA, et al. Surgical treatment of focal symptomatic refractory status epilepticus with and without invasive EEG. *Epilepsy Behav Case Rep* Sep 27, 2015;4:96–8.
- [33] Dubey D, Thodeson D, Dowling M, Sirsi D, Arnold S, Said R. Type II cortical dysplasia in dominant frontal lobe presenting as gelastic epilepsy. *Pediatr Neurol* Jul 2015;53(1):97–8.
- [34] Vendrame M, Loddenkemper T. Surgical treatment of refractory status epilepticus in children: candidate selection and outcome. *Semin Pediatr Neurol* Sep 2010;17(3):182–9.