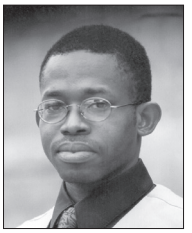
Epilepsi 2015;21(2):89-94 DOI: 10.5505/epilepsi.2015.94695

CASE REPORT / OLGU SUNUMU

Super-Refractory Status Epilepticus: An Atypical Presentation and Case-Based Review


Chiazor Udochukwu Onyia

Süper Refrakter Status Epileptikus: Bir Atipik Prezantasyon ve Olgu Bazlı Gözden Geçirme

Chiazor Udochukwu ONYIA,[1] Morenikeji A. KOMOLAFE,[2] Ayo M. ADEBIYI,[2] Olusegun OYEWOLE,[2] Fola A. FAPONLE[3]

[1]Department of Surgery, Obafemi Awolowo University Teaching Hospitals Complex, Ile-ife, Nigeria;
[2]Department of Medicine, Obafemi Awolowo University Teaching Hospitals Complex, Ile-ife, Nigeria;
[3]Department of Anaesthesia, Obafemi Awolowo University Teaching Hospitals Complex, Ile-ife, Nigeria

Summary

Super-refractory status epilepticus is known to typically arise either from a distinct underlying cause or, in patients with no history of epilepsy, from no overt cause. It has recently presented in an unclear pattern, and thus there are various challenges in its management in resource-poor settings. This case report presents a recent experience and lessons learned from a case of super–refractory status epilepticus preceded by atypical features in a 50-year-old Nigerian woman, and briefly reviews the current concepts in management of this epilepsy, especially in the context of resource-poor settings. Super-refractory status epilepticus can present with a confusing clinical picture. A good outcome in the management of this difficult problem is highly dependent on accurate diagnosis and prompt treatment. In view of the difficulties resource–poor countries have in accessing the resources and facilities required for optimal care of patients with super–refractory status, any future treatment protocols should allow for the provision of readily available therapy options in such settings.

Key words: Antiepileptic drugs; developing countries; resource-poor setting; super-refractory status epilepticus.

Özet

Süper refrakter status epileptikusun tipik olarak ya belirgin bir altta yatan nedenden kaynaklanır ya da apaçık bir neden gelişmemiş, epilepsi öyküsü olmayan hastalarda görülür. Son zamanlarda belirsiz bir hastalık kalıbı şeklinde ortaya çıkmıştır. Halen kaynakları kıt ortamlarda bu sorunu çözmeye yönelik değişik girişimlerde bulunulmaktadır. Elli yaşındaki bir Nijeryalı kadında atipik semptomlar sonrası süper refrakter status epileptikusa ilişkin güncel deneyimimiz ve çıkardığımız dersleri raporlamakta ve özellikle kıt kaynaklı ortamlarda tedavisine ilişkin güncel kavramları kısaca gözden geçirmekteyiz. Süper refrakter status epileptikus karmaşık bir klinik tabloyla karşımıza çıkabillir. Bu zor sorunun yönetiminde iyi bir sonuç elde etmek doğru tanı ve acil tedaviye bağlıdır. Kaynakları yetersiz ülkelerde süper refrakter status epileptikus hastalarının optimal tedavisi için gerekli kaynaklara ve olanaklara erişim zorluğu göz önüne alındığında, ilerde bu ortamlarda kolayca ulaşılabilir seçenekleri de hesaba katan tedavi protokolleri geliştirilecektir.

Anahtar sözcükler: Antiepileptik ilaçlar; gelişen ülkeler; kaynakları kıt ortam; süper refrakter status epileptikus.

Submitted *(Geliş)*: 14.06.2014
Accepted *(Kabul)*: 25.11.2014
Correspondence *(İletişim)*: Dr. Chiazor Udochukwu ONYIA
e-mail *(e-posta)*: shalomazor@yahoo.com

Introduction

Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 hours or more after the onset of anaesthetic therapy.[1,2] It is a severe variant of refractory status epilepticus which is defined as continuous or repetitive seizures lasting longer than 60 minutes despite treatment with a benzodiazepine together with any other standard anticonvulsant (usually phenytoin/fosphenytoin) in adequate loading dose.[1,3] It is a fairly uncommon clinical problem with high morbidity and mortality rates of up to 30% to 50%, and occurs in 10–15% of patients with status epilepticus presenting at the hospital.[2,4] Various pharmacological treatment schemes have been proposed.[1,5–7] Most of these treatment modalities are based on either observational studies or case reports.[1,5] The longer the duration of status epilepticus, the higher the risk of progression to refractory or even to super-refractory status epilepticus which may result in either death or a debilitating sequelae.[2,3,8,9] In addition, female gender and acute underlying causes including acute infections of the central nervous system have both been identified as strong factors for developing refractory illness.[10–13]

Super-refractory status epilepticus is typically encountered, though not exclusively, in two quite distinctive clinical situations.[1] First, it occurs in patients with severe acute brain injury or infection, and in patients with no history of epilepsy in whom status epilepticus (SE) develops from no overt cause.[1] This latter situation has been considered by some to be a "syndrome" referred to as NORSE (new-onset refractory status epilepticus).[1] Other conditions presenting with super-refractory status in which the aetiology of the problem is unknown include DESC (devastating epileptic encephalopathy in school-age children) and FIRES (febrile-related epilepsy syndrome).[2] Some risk factors for developing status epilepticus such as intracranial space-occupying lesions, metabolic derangements, cerebrovascular disease and sudden cessation of antiepileptic drugs have also been implicated.[14–16]

Recent studies reveal that at cellular level, movement of receptors along the surface of axonal membranes intensifies during status epilepticus, resulting in a reduction of functional γ-aminobutyric acid (GABA) receptors together with an increase in glutaminergic receptors.[2,8] This may explain why status epilepticus becomes super-refractory.[2] In addition, mitochondrial failure or insufficiency has also been identified as one possible reason behind the failure of seizure termination.[2,8] It has also been suggested that failure of seizure activity to synchronise prevents termination of seizures as observed in super-refractory status.[2] In addition, damage to the blood-brain barrier particularly in inflammatory disease has been implicated in persistence of seizures in super-refractory status.[2] No genetic mechanism has been identified yet to explain the failure of seizure termination which is characteristic of super-refractory status epilepticus.[2]

In this paper, we report our recent experience and lessons learnt from management of super- refractory status epilepticus in a middle-aged Nigerian woman while she was being managed for a central nervous system infection, followed by a review of the current concepts of care and the challenges facing it's management in resource-poor settings.

Case Report

A 50-year-old Nigerian woman of Yoruba ethnicity presented with fever of five days, headache of three days and altered level of consciousness of a day's duration. The fever was high grade, continuous and was associated with chills and rigors. The headache was generalized and throbbing. There was no associated vomiting, but the headache worsened with coughing or straining. The altered consciousness was characterized as progressively worsening drowsiness and inability to respond appropriately during conversation. There was neither any history of use of sedatives nor any ingestion of herbal concoctions.

General examination revealed an unconscious woman with a temperature of 39 °C and a vesicular peri-oral rash. Her Glasgow Coma Score (GCS) was 11/15 with eye opening (EO) of 3, best verbal response (BVR) of 3 and best motor response (BMR) of 5. She had neck stiffness with positive Brudzinski's and Kernig's signs. She also had increased tone and brisk reflexes globally. Power in all limbs was at least grade 3. Findings on fundoscopy were normal. Cardiovascular examination revealed a pulse rate of 80 per minute and a blood pressure of 130/80 mmHg. The first and second heart sounds were heard on auscultation and there were no murmurs. There were no other remarkable findings from remaining aspects of the clinical examination.

A clinical diagnosis of acute bacterial meningo-encephali-

tis was made. The differential diagnoses included herpetic meningo-encephalitis, human immunodeficiency (HIV) meningo-encephalitis and tuberculous meningo-encephalitis. Her chest x-rays were normal. Lumbar puncture was done and yielded cerebrospinal fluid that was cloudy in appearance. It contained less than 5 white blood cells/mm^3. The protein content was high (275 mg/dl) and cerebrospinal fluid (CSF) glucose was low (3.6 mmol/L). The random blood sugar (RBS) was 7.3 mmol/L. CSF microscopy showed no organisms and culture yielded no growth. The serum electrolytes, urea and creatinine results revealed bicarbonate of 23 mmol/L, potassium of 2.5 mmol/L, sodium of 136 mmol/L, urea of 5.7 mmol/L and creatinine of 80 µmol/l. Her clotting profile showed prothrombin time (PT) of 15.8 secs (with a control of 14.2 secs), international normalised ratio (INR) of 1.1, and partial thromboplastin time in kaolin (PTTK) of 24.5 secs (with a control of 22.8 secs). Her retroviral screening test was negative while electrocardiography (ECG) revealed normal sinus rhythm with no abnormality.

She was commenced on intravenous ceftriaxone at an initial dose of 2g start, and then maintained on 1g 12 hourly. She received intravenous fluids which included normal saline infusion alternating with 5% dextrose saline infusion at a rate of 1 litre 8 hourly, and was also nursed as an unconscious patient. By the 3rd day of admission, the patient had made remarkable neurologic improvement with an improved level of consciousness. The GCS was now 14 (EO of 4, BVR of 4 and BMR of 6). The fever also subsided with a temperature of 37.6 °C and she was able to ambulate out of bed.

This improvement was however sustained until the 8th day of admission when she complained of severe generalized headache which worsened on lying down. This was shortly followed by development of generalized tonic-clonic seizures which continued unabated despite administration of 10 mg of IV diazepam which was repeated 5 minutes later, as well as 300 mg of IM phenobarbitone. Her GCS rapidly dropped to 6/15 (EO of 2, BVR of 2 and BMR of 2) with the onset of the seizures, and she also had right hemiparesis. A diagnosis of vasculitis and cerebral oedema complicating the acute meningo-encephalitis was made.

Following persistence of the seizures for more than 30 minutes, she was transferred to the Intensive Care Unit (ICU) where she was intubated and commenced on assisted ventilation after the administration of 60 mg of suxamethonium, 50 mg of pancuronium followed by maintenance dose of 8 mg hourly and 75 mg of sodium thiopentone followed by maintenance dose of 50 mg per hour. IM phenobarbitone was also continued at a dose of 100 mg 8 hourly. Other drugs administered following the onset of the seizures included 800 mg of acyclovir tablets 5 times daily via nasogastric tube and IV dexamethasone at a dose of 8 mg 6 hourly. Investigation with urgent cranial CT scan revealed multiple hypodense lesions in the fronto-parietal regions bilaterally (Figure 1a, b).

Despite adequate muscle paralysis and the continuation of the anti-convulsant medications, the patient continued to have recurrent episodes of generalized tonic-clonic seizures. She had 5 episodes of the seizures with each episode lasting for about 10 minutes within the first 6 hours of admission in the ICU. This pattern continued until the

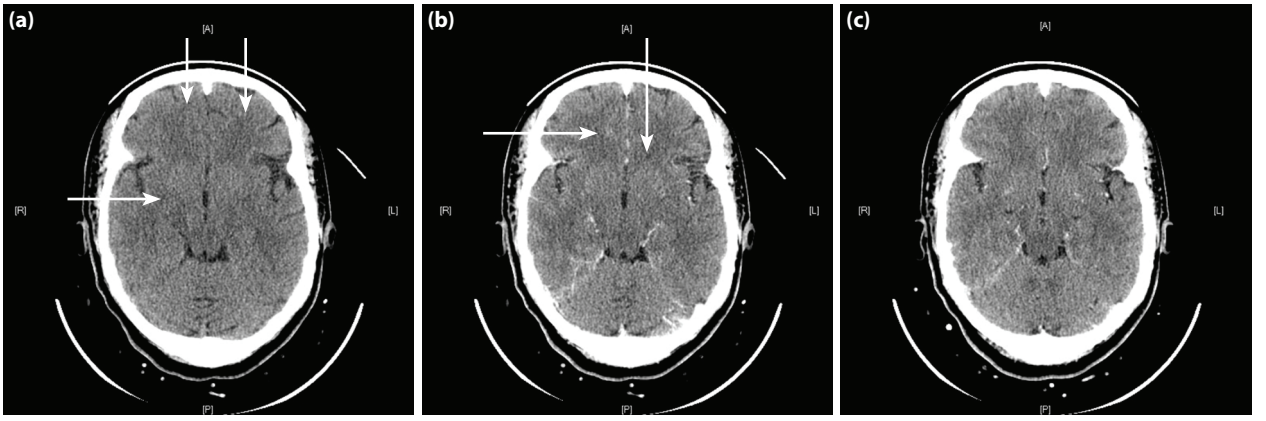


Fig. 1. **(a)** Plain cranial CT scan showing multiple hypodense lesions in the fronto-parietal regions. **(b)** Contrast cranial CT scan also revealing multiple hypodense lesions in both fronto-parietal regions. **(c)** Cranial CT demonstrating generalised cerebral edema.

3rd day of admission in the ICU when the seizures eventually resolved with gradual recovery of consciousness. She remained seizure free for 13 days. Intensive physiotherapy was commenced and she was ambulated.

Her improvement was sustained and she was subsequently discharged home on the 25th day of admission. She attends regular follow up clinic and has complaints of occasional focal seizures involving the left upper limb. She is presently on sustained release carbamazepine tablets at a dose of 200 mg twice daily.

Discussion

This patient's initial presentation was strongly in keeping with an acute bacterial or viral meningitis from which she apparently appeared to be recovering from. Both her female gender and the acute nature of her illness were clearly in support of previous findings on factors for developing refractory illness.[11,13] Bacterial meningitis and viral encephalitis have both been identified as important causes of super-refractory status epilepticus in resource-poor countries. [10,17–19] Under such inflammatory conditions, leakage of the blood-brain barrier occurs, leading to persistent excitation from ions and metabolites across the barrier.[19] The cause of her subsequent deterioration in level of consciousness coupled with the onset of the persistent seizures following initial response to therapy was however not clear, particularly since there was no associated status epilepticus ab initio, at the time of presentation. On one hand, this might perhaps have been due to vasculitis and accompanying cerebral oedema from features on cranial CT scan[11] (Figure 1a-c). On the other hand however, she was only empirically commenced on acyclovir tablets following the onset of the seizures because of the initial suspicion of viral meningoencephalitis from examination findings of perioral vesicular rash, suggesting viral herpes as a possible differential cause of the underlying problem, and eventually ended up with remarkable and sustained improvement of the seizures thereafter. Herpes simplex virus has been documented as a well known cause.[20] So, the issue now was whether a reactive vasculitis with cerebral edema or an initially undiagnosed viral encephalitis was the cause of super-refractory status epilepticus in this patient. This highlights the fact as documented in literature that a relatively common clinical mistake is to assume that such patients in whom a definite cause could not objectively be identified probably had an inflammatory condition such as 'presumed viral encephalitis' as the cause of the super-refractory status, even when no viral cause can be serologically demonstrated.[2] Shorvon et al.; postulated that a non-viral immunologically mediated condition may in fact, be the cause in such a situation.[2]

In addition to this, a major challenge encountered in her management was the handicap from lack of advanced facilities required for identification of the suspected viral causative organism, particularly as both blood and CSF cultures were negative. The importance of identifying and treating the underlying cause in the management of status epilepticus has been stressed.[1,2,6,21] Not doing so only prolongs the problem and makes the seizures more difficult to control. [1,2] Apart from carrying out the initial basic investigations based on the context (such as MRI, EEG, CSF investigations), additional work-up including metabolic and drug screen, viral serology, toxicological and auto-immune screen may all have to be considered in other to achieve this and avoid misdiagnosing the underlying cause.[2]

Apart from these limitations encountered in our management of super-refractory status epilepticus, a number of other limitations in resource-poor settings can be overwhelming and these include non-availability/exorbitant cost of intravenous antiepileptic drugs and general anaesthetic agents of first choice; exorbitant cost of intensive care facilities, exorbitant cost and non-availability of diagnostic and monitoring facilities such as serial neuro-imaging, continuous EEG monitoring and serial therapeutic drug monitoring.[8,17,22] In developing countries where both standard ICU care and anaesthetic agents currently advocated for super-refractory status such as thiopental, proporfol and midazolam may not readily available, intravenous forms of such other drugs as valproate and levetiracetam which are antiepileptic medications known to be equally effective, could be used as alternatives.[8,22] Ketamine, continous infusion of lignocaine as well as intravenous pyridoxine are other readily available, affordable and useful alternatives in such settings, as these have also been effectively used for super-refractory status though their use is not widely reported yet.[2,23,24] Both steroids which are also readily available medications and immunotherapy such as intravenous immunoglobulins have also been successfully used for super-refractory status epilepticus.[2]

Current concepts on the treatment of super-refractory status epilepticus are largely driven by evidence from observa-

tional studies since there is presently no treatment protocol yet for super-refractory status epilepticus.[1,2,6] A protocol and flowchart for the management of super-refractory status epilepticus has been suggested by Shorvon et al.[2,24] It is currently recommended that anaesthetic therapy be commenced for patients after 1 to 2 hours of persistence of the seizures.[2] This is because the onset of the cascade of harmful cellular activities leading to brain cell necrosis and apoptosis, as a result of the massive calcium influx that follows excessive glutaminergic receptor activity in seizures, often tends to start only after a few hours of continous seizure activity.[2] Furthermore, it has also been recommended that the anaesthetic agent should be administerd at a dose sufficient to achieve "EEG burst suppression" (defined as that dose just sufficient enough to suppress any EEG epileptic activity).[2,5] This is to prevent excitotoxicity effect on brain cells from persistent seizures.

With regards to when to discontinue therapy for super-refractory status, there appears to be no generally accepted consensus yet.[2] In such cases where the problem becomes prolonged, insisting on continuation of therapy has been encouraged with the aim of preventing premature withdrawal of care, particularly since there is documented experience in literature of some patients recovering after months of continous therapy.[2] In spite of this, an aggressive approach is not without challenges that could result in treatment-related complications.[23,25]

Apart from medications for therapy in super-refractory status epilepticus, useful non-pharmacological therapy exist such as controlled hypothermia which is known to act by slowing down cerebral metabolism and reducing rate of utilization of oxygen by brain cells.[2] This may not be widely available in most developing countries since it requires equipment needed for endovascular cooling. There is currently no documented reports in the literature of any studies or experience with therapeutic hypothermia for management of super-refractory status epilepticus in sub-Saharan Africa.

Reports and studies have clearly shown that ketogenic diet can be quite effective as a form of therapy for super-refractory status epilepticus.[2,7,26] Initially introduced in the 1920s for managing childhood encephalopathies, it has recently been used with success for treating the problem in adults.[7,26] It's enhanced fatty acid and restricted carbohydrate contents cause a switch in metabolism from the preferred ATP-generating pathway of glycolysis to an intermediary metabolism that results in increased production of ketone bodies, decreased glucose, and increased levels of circulating fatty acids including polyunsaturated fatty acids which have membrane-stabilizing property through marked reduction in neuronal excitability by opening of ATP-sensitive potassium channels to cause membrane hyperpolarization and through acetoacetate-mediated presynaptic release of excitatory neurotransmitters.[27,28] Unfortunately, in many developing countries, the ketogenic diet is not being utilised for super-refractory status epilepticus due to the paucity of dieticians trained to correctly calculate the components of the diet.[29] The modified Atkins form of ketogenic diet has however been proposed as a lower-cost alternative for such countries, since it does not require tedious calculations needed for the conventional ketogenic diet.[29]

Different forms of electrical and magnetic therapy have also been suggested for super-refractory status epilepsy such as deep brain stimulation, transcranial magnetic stimulation and vagal nerve stimulation.[2] These forms of therapy are thought to work by altering the synchronization of the epileptic discharges, increasing the refractory period of epileptic discharge or altering membrane or neurotransmitter function.[2] Electroconvulsive therapy has also been described with success in only a few cases of super-refractory status epilepticus.[2] However, these forms of therapy are not readily available in many resource-poor settings and most of them have not been widely accepted yet as routine options of treatment for super-refractory status epilepticus.[2]

Recommendations

Studies have clearly shown that the greatest influence on the outcome of super-refractory status epilepticus is the underlying cause.[1,2,30,31] A favourable outcome is likely with accurate and prompt diagnosis, identification and adequate treatment of the underlying cause.[1–3,30] In view of difficulties with access to resources and facilities required for optimal care of patients with super-refractory status in resource-poor settings, newer treatment protocols to be developed in the future should take into consideration some of the readily available and easily assessible options of therapy discussed. Further studies and randomized controlled clinical trials should be carried out to further objectively confirm their effectiveness.[21]

References

1. Shorvon S. Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation. Epilepsia 2011;52 Suppl 8:53–6.
2. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;134(Pt 10):2802–18.
3. Bassin S, Smith TL, Bleck TP. Clinical review: status epilepticus. Crit Care 2002;6(2):137–42.
4. Singhal A, Tripathi M. Refractory status epilepticus. Neurology Asia 2013;18(Suppl 1):67–71.
5. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 2002;43(2):146–53.
6. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135(Pt 8):2314–28.
7. Vaccarezza M, Silva W, Maxit C, Agosta G. Super-refractory status epilepticus: treatment with ketogenic diet in pediatrics. [Article in Spanish] Rev Neurol 2012;55(1):20–5. [Abstract]
8. Cherian A, Thomas SV. Status epilepticus. Ann Indian Acad Neurol 2009;12(3):140–53.
9. Logroscino G, Hesdorffer DC, Cascino G, Hauser WA. Status epilepticus without an underlying cause and risk of death: a population-based study. Arch Neurol 2008;65(2):221–4.
10. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J Neurol Neurosurg Psychiatry 2005;76(4):534–9.
11. Kastenbauer S, Pfister HW. Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in a series of 87 cases. Brain 2003;126(Pt 5):1015–25.
12. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004;351(18):1849–59.
13. Agan K, Afsar N, Midi I, Us O, Aktan S, Aykut-Bingol C. Predictors of refractoriness in a Turkish status epilepticus data bank. Epilepsy Behav 2009;14(4):651–4.
14. Nandhagopal R. Generalised convulsive status epilepticus: an overview. Postgrad Med J 2006;82(973):723–32.
15. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994;35(1):27–34.
16. Weststrate W, Hijdra A, de Gans J. Brain infarcts in adults with bacterial meningitis. Lancet 1996;347(8998):399.
17. Newton CR. Status epilepticus in resource-poor countries. Epilepsia 2009;50 Suppl 12:54–5.
18. Ogunniyi A, Ogunniyi JO, Bademosi O, Osuntokun BO, Adeuja AO. Aetiology of status epilepticus in Ibadan: a neuropathologic study. West Afr J Med 1992;11(4):263–7.
19. Friedman A, Dingledine R. Molecular cascades that mediate the influence of inflammation on epilepsy. Epilepsia 2011;52 Suppl 3:33–9.
20. Shorvon S, Tan R. Uncommon causes of status epilepticus. Epilepsia 2009;50 Suppl 12:61–3.
21. Rosenow F, Knake S. Status epilepticus in adults. Handb Clin Neurol 2012;108:813–9.
22. Tripathi M, Vibha D, Choudhary N, Prasad K, Srivastava MV, Bhatia R, et al. Management of refractory status epilepticus at a tertiary care centre in a developing country. Seizure 2010;19(2):109–11.
23. Schmutzhard E, Pfausler B. Complications of the management of status epilepticus in the intensive care unit. Epilepsia 2011;52 Suppl 8:39–41.
24. Shorvon S. The treatment of status epilepticus. Curr Opin Neurol 2011;24(2):165–70.
25. Smith M. Anesthestic agents and status epilepticus. Epilepsia 2011;52 Suppl 8:42–4.
26. Thakur KT, Probasco JC, Hocker SE, Roehl K, Henry B, Kossoff EH, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology 2014;82(8):665–70.
27. Kim do Y, Rho JM. The ketogenic diet and epilepsy. Curr Opin Clin Nutr Metab Care 2008;11(2):113–20.
28. Ma W, Berg J, Yellen G. Ketogenic diet metabolites reduce firing in central neurons by opening K(ATP) channels. J Neurosci 2007;27(14):3618–25.
29. Sharma S, Jain P. The modified atkins diet in refractory epilepsy. Epilepsy Res Treat 2014.
30. Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. Arch Neurol 2005;62(11):1698–702.
31. Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia 2001;42(11):1461–7.