"Doctor, he won't stop shaking!"

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Joshua's case:

Joshua, 44, has fallen to the ground near a bus stop. All his extremities are shaking violently. A bystander calls 911 and paramedics transfer him to the local ED. He arrives within 10 minutes and it is observed that he has a decreased level of consciousness and is sweating profusely.

On exam, his vital signs are:

- Heart rate: 110 bpm
- Respiratory rate: 24 breaths per minute
- BP: 148/96 mmHg
- Oxygen saturation: 96% on 40% oxygen by face mask
- Temperature (rectal): 37.2 C

Joshua begins seizing on transfer to a stretcher. Tonic-clonic movements are noted globally. An oral airway is inserted to protect his airway and an intravenous (IV) line is started. Joshua weighs approximately 80 kg. In a span of five minutes, 2 mg of lorazepam and 10 mg of diazepam are given intravenously. The seizure remains unchanged.

After 10 minutes, Joshua continues to seize despite receiving 4 mg of lorazepam and 20 mg of diazepam intravenously. The decision is made to perform a rapid sequence intubation using 140 mg of propofol and 120 mg of succinylcholine for induction and paralysis. Joshua is intubated without difficulty on first attempt with direct laryngoscopy.

A head CT scan is obtained, revealing no obvious abnormality. Blood tests, including a complete blood count, electrolytes, blood urea nitrogen, creatinine, international normalized ratio, CA2+ and Mg2+ are all within normal limits.

Joshua is maintained on a 8 mg/minute drip of propofol and neurology is consulted for admission and continuous EEG monitoring.

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Questions & Answers

1. How do we determine if the patient is in SE?

The widely used criterion for defining status epilepticus (SE) is continuous seizure activity lasting > 30 minutes without return to normal neurological function. This definition has been supported by results from animal studies that demonstrated significant brain damage after 30 minutes of seizing. This definition is a source of considerable controversy.

In one prospective study of 407 children presenting with a first time, non-febrile seizure, researchers were able to quantify normal seizure character and duration. The findings suggest that the likelihood of a seizure terminating spontaneously decreases substantially after five minutes and reaches a minimum at approximately 15 minutes. The authors conclude that any seizure lasting more than five minutes to 10 minutes is unlikely to terminate spontaneously and should be treated. Lowenstein, *et al* suggest that any generalized convulsive seizure lasting longer than five minutes, or more than one seizure over a brief period of time between which there is incomplete recovery of consciousness, be treated as SE.

2. What causes SE?

Despite the most common cause of SE being the discontinuation of anticonvulsant medication (especially the abrupt withdrawal of phenobarbital), over half of the patients who develop SE have no prior history of epilepsy. In pediatric populations, infectious causes account for 50% of SE cases. The acute causes of SE in adult patients are:

- Hypoxia
- Drug toxicity
- Stroke
- Alcohol intoxication
- Metabolic derangements
- Withdrawal

3. How does SE present?

The initial presentation of most patients with generalized convulsive SE is unresponsiveness and clinically overt tonic, clonic, or tonic-clonic movements of the extremities. As the seizure progresses, motor activity may become minimal and difficult to detect. However, patients may still demonstrate ictal activity on EEG. Almost all seizure types may become prolonged and manifest as convulsive or non-convulsive SE. Non-convulsive SE can have a variety of clinical presentations, ranging from subtle confusion or altered affect, to an unresponsive state lasting for hours or even days. The potential lack of clinical signs makes the diagnosis of non-convulsive SE dependant on EEG evaluation.

Table 1
First-line therapy for status epilepticus (SE)

Benzodiazepines are effective in 60% to 90% of patients as first-line therapy for SE. Benzodiazepines are potent, have a rapid onset of action and carry the risks of hypotension and respiratory suppression.

Diazepam, lorazepam and midazolam show equivalent effectiveness in terminating seizure activity, although lorazepam may have a slight advantage over diazepam due to its longer redistribution half-life. Diazepam also has the advantage of being administered rectally if IV access cannot be established. Midazolam can be administered rectally or intramuscularly (IM).

Table 2
Second-line therapy for SE

Successful seizure termination with a benzodiazepine should be followed by the administration of a long-term anti-seizure drug to prevent recurrence. Phenytoin has a prolonged anti-seizure effect after successful seizure termination with a benzodiazepine and also terminates seizure activity in up to half of the patients that do not respond to an initial benzodiazepine. Phenytoin is not used as the first-line therapy because, in this situation, it has been shown to be less effective than benzodiazepines.

A disadvantage of phenytoin is that it is suspended in a propylene glycol dilute and must be administered slowly to prevent infusion reactions. Even when administered at its maximum recommended rate of 50 mg/minute, it may cause hypotension in half of the patients and cardiac arrhythmias in a small number. Phenytoin takes effect in 10 minutes to 30 minutes after administration. Fosphenytoin is a water soluble pro-drug of phenytoin that can be safely administered quickly intravenously and IM since it does not require the propylene glycol vehicle. It achieves therapeutic levels of phenytoin more rapidly, with less infusion site reactions and has shown equal effectiveness in terminating seizure activity when benzodiazepines fail.

Barbiturates are also useful. Phenobarbital has shown equivalent efficacy to lorazepam, but has significant depressant effects on BP and the respiratory drive that can complicate management and thus, should be reserved for when benzodiazepines and phenytoin fail. However, the effectiveness of phenobarbital, after benzodiazepine and phenytoin failure, has not been clearly established and it has been suggested that the response rate may be as low as 2%.

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Table 3
Refractory therapy

Ongoing seizure activity, despite the use of two first-line agents, usually a benzodiazepine plus phenytoin or phenobarbital, is considered to be refractory to treatment. Refractory SE occurs in 9% to 31% of patients at which time anesthesia is required to control seizure activity. The administration of anesthetic medications will further depress respiratory drive and BP. Consequently, the patient should be intubated and mechanically ventilated with continuous EEG, BP and cardiac monitoring. Commonly used are propofol, midazolam and pentobarbital. There have been no prospective controlled trials evaluating the use of these anesthetic drugs in refractory SE. One retrospective review suggests that pentobarbital may have a slight advantage in terminating refractory SE, although no effect on mortality was seen. Another retrospective case series found the outcome to be independent of which coma-inducing agent is used.

4. *How should SE be managed in the ED?*

SE creates a state of physiological compromise that can be life threatening. Initial management focuses on establishing an airway, breathing and circulation and closely monitoring vital signs. Oxygen therapy should be initiated via nasal cannula or a nonrebreathing mask, an oral or nasopharyngeal device considered to maintain airway patency. If the patient is persistently apneic, or if there is an unavoidable threat to the airway, the patient should be endotracheally intubated. One also needs to establish intravenous access and initiate fluid replacement. This should be followed by determining blood glucose level and administering 50 ml of 50% dextrose intravenously and 50 mg to 100 mg of thiamine intramuscularly in hypoglycemic or apparently malnourished patients. (First-line and second-line therapies can be found in Table 1 and Table 2. Table 3 provides information on refractory therapy). Dx

For resources, please contact: **diagnosis@sta.ca**

***This department covers selected points to avoid pitfalls and improve patient care by family physicians in the ED. Submissions and feedback can be sent to* diagnosis@sta.ca.**

References
1. Shinnar S, Berg AT, Moshe SL, et al. How long do new onset seizures in children last? Annuals of Neurology. 2001. 49:659-664
2. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999. 40(1):120-122
3. Coeytaux A, Jallon P, Galobardes B. et al. Incidence of status epilepticus in French-speaking Switzerland (EPISTAR). Neurology. 2000. 55:693-697
4. DeLorenzo RJ, Pellock JM, Towne AR, et al. Epidemiology of status epilepticus. Journal of clinical neurophysiology. 1995. 12:316-325
5. Knake S, Rosenow F, Vescovi M, et al. Incidence of status epilepticus in adults in Germany: a prospective population-based study. Epilepsia . 2001. 42(6):714-728
6. DeLorenzo RJ, Hauser WA, Towne AR, et al. A Prospective, population-based epidemiological study of status epilepticus in Richmond Virginia. Neurology. 1996. 46(4):1029-1035
7. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980's. Neurology. 1993. 35:27-34
8. Hesdorffer DL, Logroscino G, Cascino G, et al. Incedence of status epilepticus in Rochester, Minnesota. Neurology. 1998. 50(3):735-741
9. Towne Ar, Pellock JM, Ko D, et al. Determinants of mortality in status epilepticus. Epilepsia. 1994. 35:27-34
10. Scott RC, Surtees RAH, Neville BGR. Status epilepticus: pathophysiology, epidemiology, and outcomes. Archives of disease in childhood. 1998. 79:73-77
11. Marx: Rosen's Emergency Medicine: Concepts and Clinical Practice. Fifth edition. 1453-1455; 2361-2354
12. Bassin S, Smith TL, Bleck TP. Clinical review: status epilepticus. Critical Care. 2002. 6:137-142
13. Walker M. Status epilepticus: an evidence based guide. BMJ. 2005; 331:673-677
14. Lowenstein DH, Alldredge BK. Status epilepticus. NEJM. 1998. 338(14):970-976
15. Nobel: textbook of Primary Care Medicine. Third edition. 1496-1497.
16. Trieman DM. The role of benzodiazepines in the management of status epilepticus. Neurology. 1990. 40:32
17. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for general convulsive status epilepticus. New England Journal of Medicine. 1998. 339(12):792-98
18. Lippik IE, Derivan AT, Horman RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA. 1983. 249:1452-1454
19. Alldredge BK, Gleb AM, Issaacs SM, et al. A comparism of Lorazepam, Diazapam, and placebo for treatment of out-of-hospital status epilepticus. NEJM. 2001. 345:631-637.
20. Rivera R et al. Midazolam in the treatment of status epilepticus. Critical care medicine. 1993. 21:991
21. Shepherd SM. Management of status epilepticus. Emergency Medicine Clinics of North America. 1994. 12:941.
22. Knapp L, Kugler A. Clinical experience with fosphenytoin in adults: pharmacokinetics, safety, and efficacy. Journal of child neurology. 1998. 13(S1):S15-S18.
23. Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Archives of neurology. 2002. 59:205-210
24. Fisher JH, Patel TV, Fisher PA. Fosphenytoin: Clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. Clinical pharmacokinetics. 2003. 42(1):33-58
25. Limdi NA, Shimpi AV, Faught E et al. Efficacy of rapid IV administration of valproic acid for status epilepticus. Neurology. 2005. 64:353-355 Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Archives of neurology. 2002. 59:205-210
26. Claassen J, Hirsh LJ, Emerson RG, et al. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002. 43:146-153
27. Rossetti AO, Logroscino G, Broomfield EB. Refractory status epilepticus. Archives of neurology. 2005. 62:1698-1702