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Approach to Neonatal Seizures

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Introduction:

Hi everyone, thank you for tuning into the latest Pedscases podcast episode. My name is Gurleen Cheema, and I am a third-year medical student at the University of Toronto. This podcast episode was created with the help of Dr. Lauren Sham, a pediatric neurologist and epileptologist and the Medical Director of the Tuberous Sclerosis Complex Program at SickKids Hospital in Toronto, Canada.

The aim of this podcast episode is to develop an approach to seizures in the neonate. Seizures are one of the most common neurologic emergencies in the neonatal period (1), with reported incidence rates ranging from 1.1 – 5.5 per 1,000 live births (2). Compared to those occurring later in infancy and childhood, approximately 85% of seizures in the neonate tend to be provoked by an acute etiology (1, 2). Therefore, it is important for medical learners to have an approach towards identifying, investigating, and treating this potentially life-threatening emergency.

The learning objectives for this episode are as follows:

Objectives:
1. Describe the clinical presentation of different types of neonatal seizures
2. Recognize that neonatal seizures can present similarly to non-epileptic neonatal behaviours and be able to contrast seizure presentations from non-epileptic behaviour
3. Identify the risk factors that predispose neonates to seizures
4. Describe common causes of seizures in the neonate.
5. Identify the different investigations to employ when working up a neonate for seizures.
6. Discuss treatment options for neonatal seizures.

Case Overview:
Let's start off by introducing a clinical case. You are working in the NICU and have been looking after baby Joe. He is a 3 day old male who was born preterm at 34 weeks gestational age and thus has been admitted to the NICU for monitoring.

The NICU nurses inform you that they have noticed Joe makes repetitive chewing or sucking motions every few minutes, even when he isn't being fed. These have been recorded in bedside logs and are noted to last approximately 30 seconds each time. They haven't noticed any body jerking or large rhythmic body movements.

What do you decide to do next? Let's review some information that may help you determine your approach to this patient.

Objective 1: Describe the clinical presentation of different types of neonatal seizures

It is important to remember that seizures in the neonate can occur with clinical manifestations or without clinical manifestations (aka electrographic only, or only seen on EEG). In fact, many neonates will have mostly or exclusively electrographic only seizures (1). This can make the identification of seizures in the neonate challenging. We will discuss later in the episode an approach to identifying neonates at high risk of seizures who should be monitored with EEG.

The International League Against Epilepsy (ILAE) has created a helpful framework for the classification of seizures in the neonate (1). A key distinction in this framework, compared with classifications used in older children and adults, is that neonatal seizures have a focal onset (1). Therefore, it is not necessary to classify neonatal seizures as generalized vs. focal (1).

The ILAE classifies seizures as electroclinical vs electrographic only. As mentioned earlier, electrographic seizures are those seen on EEG, but present without clinical manifestations. Conversely, electroclinical seizures are classified as either motor, non-motor, sequential, or unclassified (1). We will briefly discuss each of these electroclinical seizure classifications, with some examples from each category.

Motor seizures are the most common type of electroclinical seizure. They include automatisms, clonic seizures, epileptic spasms, myoclonic, and tonic seizures.

- Automatisms: these involve coordinated motor activity, typically oral behaviors such as lip smacking or chewing (1).
- Clonic: this includes repetitive jerking that involves the same muscle groups each time. These are common in neonatal stroke or cerebral hemorrhage (1).
- Myoclonic: these seizures involve sudden and brief (<100 msec) involuntary single or multiple contractions of a muscle or muscle groups. This seizure pattern is seen more frequently in infants with inborn errors of metabolism. These neonates can present with poor feeding, lethargy, and respiratory distress after an initial symptom free period of several days (1)
- Epileptic spasms: these spasms are seen more rarely but may present in neonates with inborn errors of metabolism. They present as a sudden flexion and/or extension, more commonly seen as head nodding (1).
- Tonic seizures are a sudden and sustained muscle stiffening of the limbs or trunk, and can last up to a few minutes.

Non-motor seizures are less commonly seen in neonates. They include autonomic seizures and behavioral arrest.

- Non-motor automatisms: these seizures present with alterations to the autonomic nervous system, such as apneas, cardiovascular compromise, and impaired thermoregulation (1).
- Behavioral arrests are a sudden freeze in the neonate's activity. They rarely present on their own, and more likely to be a part of a sequential seizure (1).

Sequential seizures involve events with a sequential sequence of signs, symptoms and EEG changes at different times. This type is often seen in genetic epilepsies (1).

An unclassified seizure is one presents atypically and thus does not fit in any of the above categories (1)

Let's go back to our case of baby Joe. Joe was exhibiting repetitive chewing or sucking motions every few minutes even when he wasn't being fed. This is an example of an oral automatism. You may note that this type of behaviour could present as very subtle and may be missed. How can you distinguish this behaviour from normal newborn movements? Let's go over some tips to differentiate between neonatal seizures and non-epileptic events.

Objective 2: Contrast seizure presentations from non-epileptic behaviour.

The foundation of identifying a seizure involves an understanding that seizures are generated by hypersynchronous cortical neuronal discharges. They are defined by their EEG patterns whereas non-seizure events will not have an associated seizure EEG pattern (1).

When examining a neonate that you suspect is having clonic or myoclonic seizures, check to see if you can suppress or restrain the clinical event by applying gentle pressure or repositioning the affected limb. In an epileptic seizure, the movement cannot be suppressed with pressure or repositioning. Similarly, you usually will not be able to reproduce the clinical event if it is a seizure. Conversely, non-epileptic events can often be provoked with stimulation due to reflex physiology. Both provoked and spontaneous non-epileptic events can be suppressed by repositioning or restraining the neonate (1). Examples of paroxysmal non-seizure neonatal events include (1):

- Motor automatisms that can be provoked by stimulation. This includes *episodic* chewing, swallowing, and sucking movements. Note that in Joe's case, his behaviour was recurrent, so thought to be more likely in keeping with seizure.
- Eye movements including random oscillatory eye movements and non-sustained eye deviation.
- Progressive movements, such as bicycle like movement of the legs, or swimming like movements.
- Tonic posturing, which occurs when muscles becomes stiff and rigid, with no jerking or shaking other than the sustained muscle contraction.

There are also normal newborn behaviors that may be confused for a seizure presentation. These include stretching, random sucking, and normal physiologic myoclonus that can occur during active sleep (1).

Going back to the case of baby Joe, his oral automatisms were quite repetitive in nature and occurred every few movements, even without stimulation (aka feeding).Therefore the team decided to set up video EEG monitoring and consult pediatric neurology. Note that it can be very difficult to differentiate between a seizure and non-epileptic event based off clinical suspicion alone, thus an EEG is often needed to confirm this.

Let's delve deeper in to what risk factors may be associated with neonatal seizures.

Objective 3: Identify the risk factors that increase risk of seizures in neonates.

Factors associated with increased risk of seizures in the neonatal period include (1):

- Clinical conditions that can lead to hypoxic ischemic encephalopathy (HIE). This includes as nuchal cord or cord thrombosis, low Apgar scores at time of birth, and placental abnormalities.
- Certain aspects of pregnancy, such as the presence of maternal obesity or TORCH infections in the mother.
- Newborns with a family history of epilepsy
- Newborns born at a younger gestational age, low birth weight, or with birth related head trauma. Note that Joe was a premature baby born at 34 weeks gestational age, which is a risk factor for seizures in the neonatal period.

The rest of the workup and investigations will be highly dependent on the suspected etiology of the seizure. This leads us to the next objective:

Objective 4: Describe common causes of seizures in the neonate.

Most seizures in the neonate (around 85%) are provoked (1). Common underlying causes include:
• Neonatal encephalopathy and hypoxic ischemic encephalopathy – this is the most common cause of neonatal seizures (6).
• Structural brain injuries, such as an ischemic or hemorrhagic stroke.
• Metabolic disturbances, most commonly glucose and electrolyte abnormalities.
• Acute and inborn errors of metabolism
• CNS or systemic infections
• Neonatal drug withdrawal

Although less common, it is also possible for epilepsy syndromes to present with a neonatal onset. The ILAE has broadly classified epilepsy syndromes with onset in the neonate in two major categories: self-limited epilepsy syndromes and developmental and epileptic encephalopathies (7). Although this is not the main focus of today's podcast, it is important to note that self-limited epilepsy syndromes are likely to spontaneously remit by 6 months of age

without neurodevelopmental consequences. Conversely, developmental and epileptic encephalopathies tend to be associated with developmental impairment related to their underlying genetic or metabolic etiology (7)

Objective 5: Identify the different investigations to employ when working up a neonate for seizures.

Video EEG recording is the gold standard for diagnosis of seizures in the neonate (1). For newborns at high risk of seizures, the American Clinical Neurophysiology Society recommends that video EEG monitoring be recorded for at least 24 hours (3). This presents a challenge to limited resource clinical settings, where NICU's may not have readily available access to an EEG. In this situation, the ILAE recommends using an amplitude integrated EEG, which is a bedside tool that usually displays two channels of EEG (1). In limited resource settings, it is also important to reserve video EEG for newborns at higher risk for seizures.

Additionally, all neonates presenting with seizures must have a full workup to ensure that no potential treatable etiology of the seizure has been missed. Since this may be a neurologic emergency, investigations and treatment (discussed later) should be occurring at the same time (1). Pediatric neurology should also be consulted as soon as a neonatal seizure is suspected.

Take a second to pause and think about what you would look for on a physical exam.

On general exam, you want to take the neonate's vital signs, assess their head circumference, look for birthmarks or any facial dysmorphisms, and check for signs of infection (for example – a bulging fontanelle or rash) (1). Note that signs of infection can be subtle and non-specific in newborns.

Your neurologic exam should include a measurement of their head circumference, an age-appropriate mental status exam, cranial nerve, and motor exam (1).
You will also want to order some labs (1).

• First line bloodwork investigations include checking electrolytes (sodium, glucose, calcium, magnesium), a blood gas, newborn screen if not already done, and titers for TORCH infections.

• Blood and urine cultures and toxicology screen should be ordered. All neonates presenting with seizure require a full septic workup, including a lumbar puncture. The lumbar puncture should be sent for a cell count with differential, glucose, protein, gram stain, bacterial culture, and HSV PCR. Critical diagnoses not to miss include meningitis and HSV. If suspecting an infection, draw blood cultures immediately and start the appropriate treatment simultaneously. This includes starting antibiotics at meningeal dosing as well as acyclovir to cover a possible HSV infection.

In neonates where you suspect some form of hypoxic-ischemic injury, intracranial hemorrhage,

stroke, or brain malformation, neuroimaging is required (1). As an immediate next step, a head ultrasound can be done at bedside. This can help pick up conditions like hydrocephalus or intracranial hemorrhage. MRI is the preferred imaging modality and should be considered once the neonate has been stabilized. CT is generally avoided in young children to avoid exposure to radiation.

If you have considered the above tests and are not able to identify some form of acute provoking cause of the seizure, consider performing genetic testing (1).

Returning to the case, on exam Joe was noted to present with some irritability. He did not exhibit signs of infection. When bloodwork was drawn, he was found to be hypoglycemic. An MRI was performed and had normal imaging results.

How will you manage Joe's treatment?

Objective 6: Discuss treatment options for neonatal seizures.

Seizures require emergency therapy because they can affect the neonate's homeostasis and cause brain injury. Lowering their seizure burden can significantly improve outcomes (4).

Treatment for a seizure includes both acute treatment for status epilepticus and maintenance treatment with anti-seizure medication. We will discuss both in this episode. Recall that pediatric neurology should also be consulted as soon as a neonatal seizure is suspected. Additionally, the patient should be receiving care in the NICU, as it is best equipped to handle the specialized monitoring and evaluation required for neonatal seizures.

As with any acute emergency, always start with the ABC's first – check the airway, breathing, and circulation.

Second, etiology specific treatment should be administered. This is important because some neonatal seizures may not be controlled with antiseizure medications unless their underlying etiology is treated (5). The full treatment approach to each of the possible etiologies is out of scope of this episode, but I will provide a general overview as outlined by the ILAE Task Force on Neonatal Seizures (4). Remember that in the clinical setting, much of the following decisions would be made under the guidance of pediatric neurology.

As mentioned earlier, hypoxic ischemic encephalopathy is the most common cause of neonatal seizures. These infants should be placed on therapeutic hypothermia within the first 6 hours of life if they meet criteria for cooling (4).

CNS infections such as meningitis and encephalitis are also a common cause of seizures in the neonate. These should be treated empirically with broad-spectrum antibiotics at meningitic dosing (5) as well as acyclovir for HSV depending on the clinical scenario (1).

In terms of metabolic disturbances, some common ones include hypoglycemia, hypocalcaemia,

and hypomagnesaemia. Hypoglycemia should be corrected immediately with an IV 10% dextrose solution. Hypocalcaemia should be treated with a 10% calcium gluconate IV infusion over 5-10 minutes, with a repeat dose in 10 minutes if the infant does not respond. Hypomagnesaemia is treated with a 50% solution of magnesium sulfate via intramuscular injection (5).

Once the patient has received acute treatment for status epilepticus, your next step is to determine whether they require an anti-seizure medication or not. Neonates who had a symptomatic seizure from a reversible cause (for example – an electrolyte abnormality) do not need a maintenance anti-seizure medication (5). However, if the neonate has seizures that persist despite etiology specific therapy, the medical team should consider anti-seizure medication. The first line anti-seizure medication for this situation is phenobarbital (4).

In the case of baby Joe, his hypoglycemia was corrected with an IV solution of 10% dextrose He did not have any recurrent seizures after the glucose correction and thus was not started on a maintenance anti-seizure medication.

What happens after you administer treatment?
Now, you monitor response to treatment with an EEG (5). If the neonate is not responding to treatment, reconsider your differential for any missed seizure etiologies. The second line treatment for neonates not responding to first line medications includes phenytoin, levetiracetam, midazolam, or lidocaine (4). These decisions would be made under the guiadnace and evaluation of pediatric neurology at most institutions.

How do you decide if the patient needs to continue their anti-seizure medication before hospital discharge?
For patients who had an acute provoking cause of their seizure, their anti-seizure medication can be safely discontinued before discharge (4). However, this differs for patients in which neonatal onset epilepsy syndrome is diagnosed as they will likely require long term treatment. They will have an ongoing risk for seizures and should be continued on a maintenance dose of phenobarbital after discharge, with close follow up. Their parents should be counselled on the different signs and symptoms of infantile seizures so that they can seek urgent care if needed (4).

In the case of Joe, because he had an acutely provoked seizure, he was monitored in the NICU with EEG until he had a seizure-free period of 72 hours. At this point, his phenobarbital was discontinued and he was discharged home.

Conclusion and Summary:

This brings us to the end of our case. Let's summarize a few of the key learning points from this podcast:

1) Neonatal seizures are always focal in onset. However, they may be classified as electrographic only or electroclinical. Within electroclinical seizures, motor seizure types are the most common. However, seizures in the neonate may be missed as they may present very subtly.

2) Given that neonatal seizures may present subtly, it is important to distinguish them from non-epileptic events. A key differentiating feature is that a true seizure in the neonate cannot be suppressed or provoked with stimulation.
3) Some common risk factors for neonatal seizures include hypoxic ischemic injury, maternal TORCH infection during pregnancy, birth related head trauma or other brain injury, and a a family history of epilepsy.
4) The vast majority of neonatal seizures are provoked. The most common cause is hypoxic ischemic encephalopathy, but other causes include structural brain injuries, metabolic disturbances, inborn errors of metabolism, infection, and drug withdrawal.
5) The gold standard investigation for diagnosing a seizure is video EEG. However, an appropriate workup to investigate any underlying treatable cause of the seizure must also be employed. This includes checking electrolytes, a full septic workup with lumbar puncture, blood and urine cultures, as well as toxicology screen. Neuroimaging should be ordered if suspecting brain injury.
6) Management is guided by pediatric neurology and includes stabilizing the neonate and treating any underlying etiologies. If seizures persist despite treating the underlying cause, the first line anti-seizure treatment to be used in the neonate is phenobarbital.

By the end of this episode, I hope you have a greater understanding of how to identify seizures and differentiate them from non-seizure events, order appropriate investigations for neonatal seizures, and employ appropriate treatment strategies. Thank you for listening!

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