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TEACHING FILES (GRAND ROUNDS)

NOT ALL SEIZURES ARE EPILEPTIC: A NEONATAL CASE OF HYPEREKPLEXIA

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Clinical Problem:
A full-term male newborn was delivered via vacuum extraction to non-consanguineous parents following a monitored pregnancy. He presented risk factors for infection, including maternal colonisation of group B Streptococcus and a urinary tract infection during the third trimester. A few hours after birth, he developed generalised hypertonia, feeding difficulties, abnormal posturing - including chewing-like movements and marked cervical hyperextension. Although these symptoms were initially suspected to be neonatal seizures, they did not respond to prompt treatment with phenobarbital and levetiracetam.

The newborn was transferred to a Neonatal Intensive Care Unit (NICU) where he remained stable but continued to exhibit the same findings. He displayed exaggerated startle reflexes triggered by minimal stimuli, preserved consciousness and sleep-specific myoclonus. While the EEG was not available, other causes such as infections, structural anomalies and metabolic disorders were discarded. Then, an EEG was performed and revealed episodes of startle without epileptiform activity. A clinical diagnosis of hyperekplexia was considered and clonazepam was initiated, providing relief from the symptoms. However, occasional Vigevano manoeuvres were required to manage episodes of hypertonia.

What clinical features and investigations enable clinicians to reliably distinguish neonatal hyperekplexia from seizures and other causes of neonatal hypertonia and how does this distinction influence immediate management strategies?

Discussion:
Hyperekplexia is a rare, non-epileptic paroxysmal disorder characterized by three cardinal signs: exaggerated startle reflexes, caused by trivial stimuli, such as percussion of the trigeminal area (for example, tapping the glabella), which resist habituation; generalised hypertonia (which can lead to central apnoea - due to dysfunction of the brainstem - or peripheral apnoea - due to rigidity of the respiratory muscles) with maintenance of the state of consciousness and no post-ictal period; and myoclonus can also be observed, which can be repetitive and intense, especially during deep sleep.[1,2] Hypertonia tends to resolve over time.[1] There are no generalised or lateralized tonic movements.[1,2,3,4]

The aetiopathogenesis seems to be related to errors in the glycine receptor, which is essential for inhibitory neurotransmission in the brainstem. These errors may be hereditary (associated with mutations in genes such as GLRA1, GLRB, SLC6A5, GPHN and ARHGEF9), sporadic (occurring in individuals with no family history or clear genetic basis), or acquired (due to conditions like post-hypoxia, encephalitis, multiple sclerosis, neurodegenerative or neurometabolic diseases and paraneoplastic syndromes).[1,2] This makes the differential diagnosis challenging, as secondary causes must be discarded. Hereditary hyperekplexia can manifest as early as the third trimester of pregnancy with abnormal movements or later, such as in the neonatal period and even in adulthood.[1,2] While over 200 cases have been documented, its true prevalence remains uncertain.[2] In this case, we reported a case of a neonate who presented feeding difficulties secondary to generalised hypertonia, progressing to asymmetrical posturing, chewing-like movements and cervical hyperextension, within the first 24 hours of life. Notably, these episodes were consistently triggered by unexpected stimuli, occurred with unaltered consciousness and showed no habituation. Myoclonia was noted during sleep but not while awake. EEG monitoring during startle episodes confirmed non-epileptic activity without ictal patterns. The diagnosis is mainly clinical.[1] Although the initial diagnosis was presumed to be neonatal seizures, a non-epileptic paroxysmal disorder was considered early in the differential diagnosis. His clinical suspicion was reinforced by ancillary investigations, which excluded other potential causes, including infectious, structural and epileptic aetiologies. However, the definitive diagnosis of hyperekplexia was achieved by identifying two pathogenic heterozygous variants of the GLRA1 gene, associated with Hereditary Hyperekplexia type 1. Each variant was inherited from one parent, following an autosomal recessive pattern.

Treatment for hyperekplexia mainly involves clonazepam, a gamma-aminobutyric acid (GABA) receptor agonist.[1,2,3,4] This medication helps alleviate the dysfunction of the chloride channel associated with glycine activity and provides anxiolytic benefits.

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Other medications, such as phenobarbital, diazepam and sodium valproate, have not effectively prevented or reversed the episodes.[1] At the onset of the condition and while the hypothesis of neonatal seizures seemed more likely, phenobarbital and levetiracetam were administered on three occasions, with no improvement in the condition. However, when clonazepam therapy was started, there was a reduction in the number of episodes of hypertonia. In cases of prolonged hypertonia with a risk of apnoea, Vigevano's manoeuver—forced flexion of the head and lower limbs toward the body—can be life-saving.[1,2] Clinicians should maintain a high index of suspicion for hyperekplexia in newborns who present with hypertonia and do not respond to conventional anticonvulsants. Early recognition is vital to avoid misdiagnosis, inadequate treatment and adverse outcomes.[1,2] Clonazepam is the treatment of choice and educating carers about the Vigevano manoeuvre can save lives.[1]

Compliance with ethical standards
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