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Case Report
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Intractable Neonatal Hyperekplexia: A Case Report

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Abstract

Abnormal movements are not uncommon in neonates. These could be either seizures or seizure mimics. The neonatal physician has to recognize it as early as possible to initiate appropriate management. Hyperekplexia is one of the rare but treatable causes of seizure mimics in neonates. It is characterized by short and episodic periods of generalized tonic spasms in response to unexpected auditory, acoustic or any form of tactile stimuli. Hyperekplexia is diagnosed mainly by its classical clinical features. Nose tapping test is the bed side clinical method which can help the diagnosis of Hyperekplexia. At times they are at risk for sudden death due to life threatening apnea, sudden infant death syndrome, aspiration and cardiopulmonary arrest due to intractable tonic posturing during sleep. The tonic spasms of hyperekplexia can be ceased by Vigevano maneuver. It is done by the forced flexion of the head and legs towards the trunk during the episode of severe tonic spasms associated with respiratory impediment. This is a lifesaving manoeuvre which has to be taught to the care givers especially before discharge. We hereby present a case of intractable neonatal hyperekplexia with severe repeated tonic spasms and apnea, which was resistant to clonazepam treatment. Later on, tracheostomy was needed due to apnea and prolonged ventilation. The baby however died at the age of 14 months.

Keywords: Neonatal, Hyperekplexia. Exaggerated Startle Reflex, Startle Syndrome, Tonic Spasms.

Case Presentation

A 2 months old female infant presented to pediatric emergency department with history of episodic attacks of apnea with cyanosis and tonic spasms lasted for few minutes which was aborted spontaneously. Within few hours of admission, she developed tonic spasms, apnea, desaturation and bradycardia. She was treated with iv phenobarbitone. Again, she developed another episode of apnea with stiffness and was intubated and shifted to Intensive care unit. On eliciting the history from the mother, the symptoms started after 2 days of birth and interestingly each episode was precipitated by auditory or tactile stimuli. Several attacks occurred on daily basis since birth. Parents sought various medical advice in the private but no active treatments were suggested and reassurance was given.

She was born to a nonconsanguineous parents as a full term normal vaginal delivery with APGAR score of 9 and 10 at 1 and 5 minutes respectively. The birth weight was 2.4 kg. She had poor sucking, irritability, poor weight gain and delayed developmental mile stones. She has family history of similar tonic spasms, apnea and cyanosis precipitated by tactile stimuli in her female cousin from paternal side who had spontaneous resolution of the symptoms by one and half years of age and she is currently doing well.

She was admitted to the pediatric department initially and was treated with phenobarbitone, antibiotics and ant reflux medications without any improvement in her clinical status. She continued to have severe tonic spasms with prolonged apnea, multiple episodes of cardiac arrest and was revived with full resuscitation and intubation. By the age of 3 months, she was transferred to neonatal intensive care unit due to her low weight. Her physical examination revealed failure to thrive, exaggerated startle reflexes and tonic spasms of the limbs with any form of tactile or auditory stimulation. Hernial orifices were free, systemic examination were normal and no other abnormalities detected. With the history and clinical findings nose tapping test was performed. This test revealed a bilateral flexor response of upper limb, flexion of knees with a classical blink without habituation. Her complete blood count, septic evaluation, electrolytes, calcium, magnesium, glucose, coagulation profile, CSF studies, metabolic screen including amino acid profile, organic acids,

keto acids and glycine were normal. Brain MRI showed diffuse cerebral and brain stem encephalomalacia [Fig 1] secondary to hypoxic ischemic encephalopathy possibly due to repeated hypoxic effects. EEG showed a burst suppression pattern due to diffuse encephalopathy [Fig 2]. During the EEG recording she had three episodes of tonic spasms which was not associated with any EEG changes. Pediatric neurology opinion was obtained and the diagnosis of hyperekplexia was confirmed.

Based on the typical history, clinical examination, normal laboratory investigations and radiological examination she was diagnosed to have Hyperekplexia. She was treated with low dose of clonazepam initially and the dose was increased gradually to 1mg per day. Tonic spasms were controlled only partially. Levetiracetam and pyridoxine were added but was stopped after few weeks as there was no response. Several trials of extubation failed and she needed further ventilatory support and finally ended with tracheostomy. Overtime she became less responsive and had minimal spontaneous movements(hypokinesia). She continued to have episodes of tonic spasms, apnea and cyanosis even while changing the diapers. Family refused for molecular genetic analysis. She was ventilator- dependent and died at the age of 14 months due to sepsis.

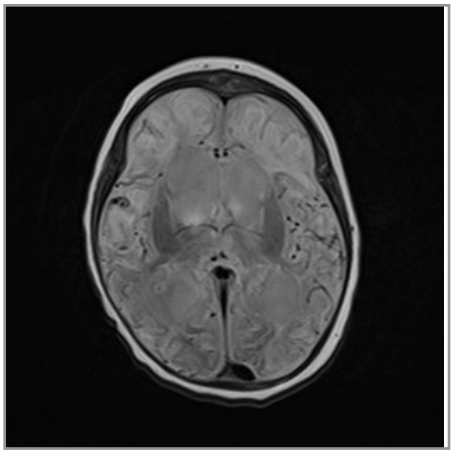

Figure 1: MRI Brain Shows Diffuse Encephalomalacia

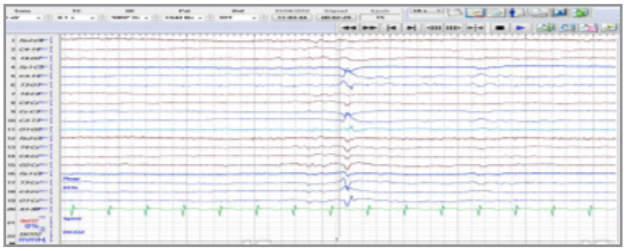

Figure 2: EEG Shows Burst Suppression Pattern

Discussion

Hyperekplexia: Hyperekplexia is a Greek word which means "to jump excessively". It was first described by were the first to use the term "hyperexplexia" which was later on corrected by [19,20]. At least 150 cases have been reported so far. Other names mentioned in the literature are Congenital stiff-man syndrome, Familial startle disease and Surprise disease [17,18].

Startle syndrome is the term used to denote varied disorders characterized by an abnormal reaction to the normal startle phenomena. Hyperekplexia is one of the well described startle syndromes.

Normal Startle Reflex: The typical pattern of normal startle reflex is bilateral symmetrical flexion response with a constant blink due to involvement of cranio-cervical muscles, especially the orbicularis oculi. The complete presentation involves forward flexion of the head with a blink, defensive flexor posture of elbows and knees, bduction of the shoulder with minimal movement of the trunk. The well-studied stimuli for this response are auditory with sound level of at least 80 Db. The normal startle response habituates with in one to five trials of auditory stimuli, leaving only the auditory blink reflex [3-4].

Exaggerated startle reflex: It can be differentiated from the normal startle reflex by its lower threshold, much severe form, failure of habituation and the likelihood of lower limb involvement [4, 21].

Hyperekplexia is a non-epileptiform disease characterized by abnormal response to any unexpected stimuli in the form of exaggerated startle reflex, short period of generalized tonic spasms and rigidity [1-2 ,16].The onset can even start in the fetus and manifest as abnormal intrauterine fetal movements [16].Pediatric and rarely adult-onset disease has been described.

It is classified into hereditary, sporadic and symptomatic hyperekplexia according to the cause and onset of the disease (Table 1) [5].

Table 1: Classification of hyperekplexia

Hereditary Hyperekplexia Major form Minor form
Sporadic hyperekplexia Idiopathic onset
Acquired Hyperekplexia Causes 1.Cerebral palsy 2.Postanoxic encephalopathy 3.Brainstems infarcts 4.Posterior fossa malformations

Hereditary Hyperekplexia: It is a rare genetic non epileptic neurological disorder with the usual neonatal onset. It is characterized by exaggerated startle responses, tonic spasms, neonatal hypertonia and positive nose tapping test which is the hall mark of this disease. The prevalence of the disease has been estimated to be less than 1 in 100,000.

Genetic Basis: It occurs due to mutation in the gene involved in the function of neurotransmitter glycine. Majority of the cases are autosomal dominant. There are at least 5 genes reported as a cause of hereditary hyperekplexia. Different nonsense, missense and frameshift mutations in the alpha sub unit of glycine receptor gene (GLRA1) has been identified in majority of the cases [6]. Recently recessive mutations in the gene encoding presynaptic glycine transporter 2 (SLC6A5) has been identified as the second major cause [7].

Classification: Hereditary hyperekplexia is classified as major or minor [8]. Diagnosis is mainly clinical with supportive positive family history and can be confirmed with molecular genetic analysis.

(A) Major forms: It includes the following clinical features,

1. Generalized hypertonia particularly in an awake state.
2. Exaggerated startle responses.
3. Brief tonic spasms which may mimic generalized tonic seizures.
4. Apnea and cyanosis following tonic spasms.
5. Myoclonic jerks [9, 10].

Out of five at least three features should be present for the diagnosis of major form. Our case has 4 features qualifies for major form.

Clinical Signs for Diagnosing Major forms: Following clinical signs may help to reach the diagnosis of major forms.

- Nose tapping test: Tapping the tip of nose or fore head consistently produce generalized flexor spasms without habituation is the hall mark of the disease. There won't be any response in a normal baby [22].
- No change in the posture while holding the neonate in vertex or horizontal plane [11].
- Moro reflex: Normal extension of arms is replaced by flexion as startle response.
- Other than startling and stiffness, hall mark of hyperekplexia in stiff neonates is the head retraction reflex. It consists of a brisk involuntary backward jerk of head often associated with retraction [12].

(B) Minor forms: Have startle responses being more than the normal but without any above-mentioned features.

Associated features mentioned in various literatures are: Nocturnal myoclonus, increased incidence of developmental dysplasia of hips, hypokinesia, feeding difficulties, delayed mile stones, umbilical hernia and low intelligence [16, 19]. Spontaneous resolution of hypertonia occurs by 1-3 years in majority of the cases [22]; however, the exaggerated startle reflex may persist to adulthood leading to frequent falls [14].

Positive Family history, irritability, poor feeding, delayed developmental milestones and apnea were described in various cases as was present in our case. S.D Sharma et all described a case of neonatal hyperekplexia with onset at 2 days of life and delayed mile stones like our case [16]. Sudden infant death syndrome (SIDS) is being well reported in Hyperekplexia [13]. Central apnea due to brain stem dysfunction or peripheral apnea with aspiration after feeding could be are the probable mechanisms of death in SIDS [14]. McAbee GN et all reported a case of complete heart block in non-familial hyperekplexia [25].

Severe neonatal form was described characterized by repeated nocturnal myoclonus, hypertonia with life threatening apnea due to contraction of the respiratory muscle as reported in our case [16]. Cases with Hernia possibly due to persistently elevated intra-abdominal pressure due to tonic spasms and Developmental dysplasia of hips were reported but were not found in our case [19, 26]. Cases with hypokinesia were reported as was in our case which happened in the later stage [16]. Risk of death from apnea can be aborted by forced flexion of the head and legs over the trunk as reported by [15.22].

Diagnosis: Diagnosis is mainly by clinical.EEG is usually normal. Electromyography shows a
characteristic almost permanent muscular activity with periods of electrical quietness [27]. Electromyography can be used to monitor treatment and identify minor hyperekplexia [4].Molecular genetic studies are the confirmatory for Hereditary hyperekplexia [7].

Treatment: In hyperekplexia the most troublesome symptom is tonic spasms. Even though the evidences are limited, the most consistent effects are with clonazepam, considered as a drug of choice. It binds directly to the alpha 1 sub unit of GABA receptor and potentiates the inhibitory effects. Clinically it reduces the frequency and magnitude of the startle responses. Clonazepam is indicated only when the symptoms are troublesome and impairs daily activities. Dose can be adjusted from 0.5 mg to 1 mg per day. Valproic acid, 5 hydroxy tryptophan and piracetam have been tried with some effects. Vigabatrin have been studied and said to be ineffective [14].

Vigevano maneuver: The tonic spasms can be stopped by forced flexion of the head and legs towards the trunk, which could be a lifesaving one. Mother has to be taught about this maneuver be-

fore discharge [15]. Hyperekplexia has to be differentiated from all other causes of neonatal hypertonia with the classical history, clinical presentation and importantly the stimulation test by tapping the nose, fore head or upper lip.

Differential Diagnosis Includes

1. Neonatal tetanus.
2. Apneic spells.
3. Tonic seizure.
4. Neonatal drug withdrawal syndrome.
5. Spastic quadriplegia.
6. 6Startle provoked epileptic seizures (Startle epilepsy).
7. aysachs disease (a cause of exaggerated startle reflex) [8, 23, 24].

Due to advances in the molecular understanding of hyperekplexia, screening for mutations in GLRA1 should be opted in the presence of positive family history and if this gene is negative other gene mutation studies like SLC6A5 can be performed.

Declaration of Interest

The Authors declare that there is no conflict of interest.

Conclusion

1. The treating clinician should have a high index of suspicion whenever there is a neonate with episodic hypertonia precipitated by any kind of stimulus, as early diagnosis is important in initiation of treatment and prevent complications.
2. Vigevano maneuver could be lifesaving if initiated at an appropriate time
3. Molecular gene diagnosis will help in difficult cases.

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