CASE REPORT

Sinus Node Paucity in Hyperekplexia

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We report a newborn with hyperekplexia and uncontrolled tonic spasms which did not respond to intravenous phenobarbitone and phenytoin, and midazolam infusion. Serum biochemistry, electrocardiography, electroencephalography, lumbar puncture and neuroimaging were normal. Continous cardiac monitoring revealed that tonic spasm episodes were accompanied by sinus node paucity and severe bradycardia. Duration and number of tonic spasm episodes decreased with clonazepam therapy, and she was discharged. At 4 months of age sudden infant death occured. Sudden infant death could be related to the paucity of sinus node. Cardiac pacemaker implantation should be considered even if the medical treatment is successful.

Key words: *Hyperekplexia, Neonate, Seizures, Sinus node.*

Hyperekplexia or Startle disease is a rare, sporadic or autosomal dominant disorder that with variable expression(1). Most patients present in the neonatal period; clinical picture is characterized by myoclonic jerks, increased muscle tone, tonic spasms, generalized hyperreflexia and severe apnea without concomitant discharges on electroencephalography (EEG). This disorder is frequently misdiagnosed as convulsion in neonatal period.

Life-threatening tonic spasm episodes associated with severe apnea and bradycardia may occur. These episodes may result in sudden death(2-5). Although cardiac irregularities - such as bradycardia, tachycardia, and complete heart block, have been demonstrated in hyperekplexia, sinus node paucity has not been reported. We report a newborn with the sporadic form of hyperekplexia who had episodes of tonic spasms accompanied by sinus node paucity and severe bradycardia.

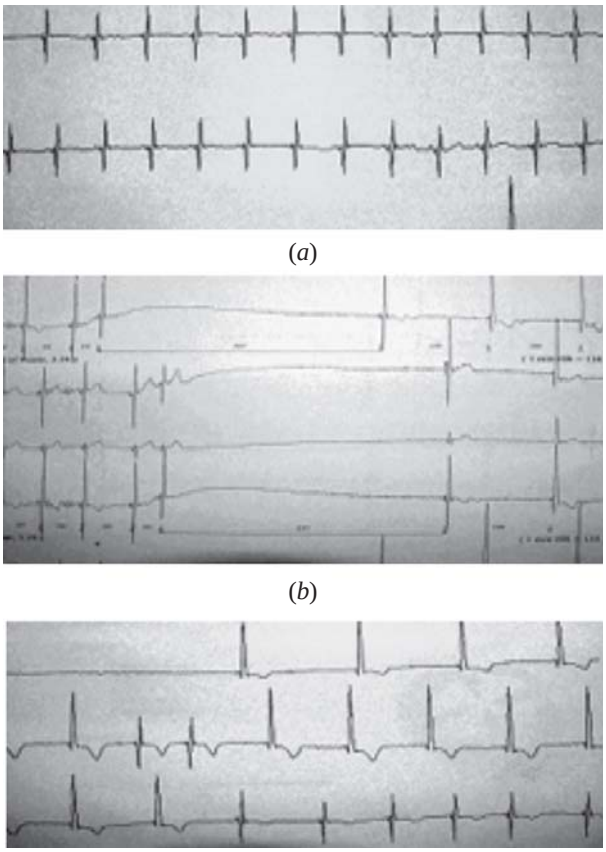
CASE REPORT

A girl born at term by cesarian section, with a birth weight of 3000 g had Apgar score of 7 and 8 at 1 and 5 minutes. Her parents were unrelated and she was the first child. There was no history of prenatal alcohol or drug use. The child was noticed to have exaggerated startle and Moro reflex during first few hours of life. This was associated with generalized hypertonicity, hyperreflexia, and tonic spasms, mimicking tonic seizures lasting up to 5-10 seconds and leading to feeding difficulties. Phenobarbital, phenytoin and midazolam infusion were started, in that order, to control the seizures. Serum amino and organic acids, serum lactate and pyruvate concentrations, lumbar puncture, EEG and cranial magnetic resonance imaging and cranial computed tomography were normal. Since there was no resolution of symptoms and spasms continued, the infant was transferred to our hospital on postnatal day 25. Family history was negative for epilepsy and symptoms of hyperekplexia.

Examination on admission revealed an alert infant with exaggerated startle reflex, generalized hypertonicity and hyperreflexia. She was normal at sleep. Nose tapping resulted in retraction of the head, followed by flexor spasm of all extremities and exaggerated startle lasting up 10 seconds, without habituation. The hemogram, serum electrolytes,

ammonia, lactate dehydrogenase level, serum lipid levels, serum lactate and pyruvate, lumbar puncture, cultures from blood, urine, cerebrospinal fluid, multiple electro-encephalographies (EEG), brain computed tomography and magnetic resonance imaging, electromyography and echocardiography were all normal. Midazolam, phenobarbital and phenytoin were of no benefit and were discontinued and clonazepam was started at a dosage of 0.1 mg/kg/day. Flexion of head and lower extremities toward the trunk was beneficial.

Some stiffening episodes were accompanied by bradycardia and desaturation of arterial oxygen saturation. Continuous cardiac monitoring demonstrated an average baseline heart rate of 138/min (range: 114-165/min) (***Fig.1a***). Episodes of stiffening spasms followed by bradycardia leading to paucity of sinus node nearly to 3.6 seconds, followed by a junctional atrial escape rhythm at 54-65/min., were recorded 13 times in a 24-hour period (***Fig. 1b,c***). Bradycardia as low as 20/min during episodes was associated with desaturation of arterial oxygen measured by pulse oxymetry (SaO_2 50%; baseline oxygen saturation: 95-100%). Not all bradycardic episodes were associated with apnea. A cardiac pacemaker insertion was discussed but because of a decrease in number and duration of these episodes after clonazepam therapy, cardiac pacemaker was not inserted. She was dicharged on day 65 with clonazepam and orogastric tube feeding. At age of 4 months, sudden infant death occurred.



(*a*)

(*b*)

(*c*)

FIG.1 *Electrocardiogram rhythm strip from Holter monitor. (a) baseline rate of 138/min; (b) onset of tonic spasm associate with sinus node paucity duration of 3.6 seconds; (c) junctional atrial escape rhythm with rate of 54-65/min and rate returns to 135/min.*

DISCUSSION

Hyperekplexia is a rare and generally benign disorder. Shahar and Raviv(6) reported 39 children diagnosed as sporadic major hyperekplexia presenting at an average of 3.3 months and treated with low doses of oral clonazepam. All of them recovered. But sometimes hyperekplexia may become life-threatening, leading to sudden infant death if not promply diagnosed and treated accordingly.

The underlying pathophysiology of tonic spasms in hyperekplexia is controversial. In 30% of patients with familial hyperekplexia several mutations in the alpha-1 subunit of the glycine receptor linked to chromosome 5q33-35 have been reported(7). Family history was negative for familial hyperekplexia, and we did not investigate the mutation analysis of glycine receptor. As an inhibitory neurotransmitter, glycine plays an important role in the neuronal regulation of muscle tone in the brain stem and spinal cord. Once released from the presynaptic vesicles, glycine binds to the α-1 subunit of glycine receptor, which causes the channel to open for Cl^-, thus hyperpolarizing the postsynaptic cell. Selective blockade of glycinergic inhibition by strychnine or by tetanus toxin results in excessive startle, and massive spasms of the trunk and limbs. Correspondingly, mutations of the α1 subunit of the glycine receptor cause a variety of dysfunctions of the Cl^- channel, therefore, is regarded as a channelopathy(8). Decreased concentrations of the inhibitory α-aminobutyric acid have been also detected in

cerebrospinal fluid in infants with hyperekplexia(9). In addition, response to central α-aminobutyric acid-benzodiazepines agonist such as clonazepam implies a possible role for overflow of abundant excitatory bioamines in the pathophysiology of hyperekplexia(6). The underlying pathology of sudden infant death syndrome, apnea, and cardiac irregularities such as bradycardia and complete heart block in hyperekplexia is speculated as brainstem-generated autonomic dysfunction(4,9).

Cardiac irregularities; such as bradycardia, tachycardia, and complete heart block, have been reported in hyperekplexia(3,9,10). McAbee, *et al.*(10) reported a newborn with tonic spasm episodes associated with prolonged apnea and complete heart block requiring the implantation of permanent cardiac pacemaker. Sinus node paucity has not been reported in hyperekplexia. Sinus node paucity occurs in infants with cardiac structural abnormalities, especially in sinus venosus defects, and after atrial surgery. Our infant had no evidence of structural cardiac disease. Cardiac pacemaker can be effective in minimizing the risk of sudden death from paucity of sinus node(11). A cardiac pacemaker insertion was discussed but because of a decrease in number and duration of these episodes after clonazepam therapy, cardiac pacemaker was not inserted. She was discharged on day 50 with clonazepam and orogastric tube feeding, sudden infant death occured at 4 months of age. Close cardiac monitoring and cardiac pacemaker implantation could have averted the sudden infant death.

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