

# Hyperekplexia in neonates

V Praveen, S K Patole, J S Whitehall

## Abstract

**Hyperekplexia (startle disease) is a rare non-epileptic disorder characterised by an exaggerated persistent startle reaction to unexpected auditory, somatosensory and visual stimuli, generalised muscular rigidity, and nocturnal myoclonus. The genetic basis is a mutation usually of the arginine residue 271 leading to neuronal hyperexcitability by impairing glycinergic inhibition. Hyperekplexia is usually familial, most often autosomal dominant with complete penetrance and variable expression. It can present in fetal life as abnormal intrauterine movements, or later at any time from the neonatal period to adulthood. Early manifestations include abnormal responses to unexpected auditory, visual, and somatosensory stimuli such as sustained tonic spasm, exaggerated startle response, and fetal posture with clenched fists and anxious stare. The tonic spasms may mimic generalised tonic seizures, leading to apnoea and death. Consistent generalised flexor spasm in response to tapping of the nasal bridge (without habituation) is the clinical hallmark of hyperekplexia. Electroencephalography may show fast spikes initially during the tonic spasms, followed by slowing of background activity with eventual flattening corresponding to the phase of apnoea bradycardia and cyanosis. Electromyography shows a characteristic almost permanent muscular activity with periods of electrical quietness. Nerve conduction velocity is normal. No specific computed tomography findings have been reported yet. Clonazepam, a gamma aminobutyric acid (GABA) receptor agonist, is the treatment of choice for hypertonia and apnoeic episodes. It, however, may not influence the degree of stiffness significantly. A simple manoeuvre like forced flexion of the head and legs towards the trunk is known to be life saving when prolonged stiffness impedes respiration.**

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## History

Hyperekplexia, or startle disease, is a rare non-epileptic disorder characterised by an exaggerated persistent startle reaction to unexpected auditory, somatosensory, and visual stimuli, generalised muscular rigidity in infancy, and nocturnal myoclonus.<sup>1,2</sup> After its first description in 1958 by Kirstein and Silfverskiold, more than 150 cases of hyperekplexia have been reported so far.<sup>3,4</sup> In 1966 Suhren *et al* reported a family of 24 individuals with this disorder which he named hyperexplexia (Kok's

disease) after the Greek word for startle.<sup>5,6</sup> A year later Gastaut and Villeneuve reported 12 patients without a family history of exaggerated startle and corrected the Greek spelling to hyperekplexia which has been adopted since.<sup>7</sup>

## Introduction

Startle reflex, a normal reticular and cortical reflex is elicited to a minor degree in normal newborns and infants.<sup>8</sup> It is a basic alerting reaction consisting of facial grimacing with blinking, followed by involuntary movements of head flexion, hunching of shoulders, adduction of the arms, and flexion of the trunk and the knees, causing falling without a protective reaction.<sup>9,10</sup> It appears in infancy at the same time as the Moro reflex, and becomes more noticeable as the Moro reflex disappears.<sup>11</sup> When a pathologically exaggerated startle response interferes with normal activities, causing apnoea and frequent falls and injuries, the pathological state is termed as startle disease or hyperekplexia.<sup>3,10</sup> Hyperekplexia may occur in a minor form in which the startle response is exaggerated from normal, or a major form in which patients present with generalised muscular rigidity during the neonatal period.<sup>12</sup>

## Aetiology

The aetiology of hyperekplexia is not clear. Hyperactivity of cortical neurons, abnormalities of the inhibitory systems of the brain, and abnormalities of the serotonergic pathways are among the proposed mechanisms.<sup>13-16</sup> Experimental data suggest the importance of nucleus gigantocellularis in the pathogenesis of the abnormal startle response.<sup>17</sup> Subtle brainstem vascular anomaly, pontine infarct, lacunar posterior thalamic-subthalamic infarcts, and brainstem encephalopathy have been reported in adults with hyperekplexia.<sup>18-21</sup> Hyperekplexia is also reported in adults after mild to moderate head injury as part of post-traumatic movement disorder.<sup>22</sup>

## Genetic basis

Hyperekplexia is usually familial, most often autosomal dominant with complete penetrance and variable expression.<sup>23</sup> Autosomal recessive form and sporadic cases have also been described.<sup>24</sup> The genetic basis is a mutation usually of the arginine residue 271, transforming  $\beta$  alanine and taurine in the glycine receptor from agonists into competitive antagonists.<sup>25,26</sup> This change affects chloride conductance of the  $\alpha$ -1 subunit of the inhibitory glycine receptors in the caudal pontine reticular formation leading to neuronal hyperexcitability by impairing the glycinergic inhibition.<sup>27-29</sup> Recently linkage analysis has

Department of  
Neonatology, Kirwan  
Hospital for Women,  
Townsville, QLD 4817,  
Australia  
V Praveen  
S K Patole  
J S Whitehall

Correspondence to:  
Dr Patole  
SANJAY\_PATOLE@  
health.qld.gov.au

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mapped a gene for this disorder to chromosome 5q33–q35.<sup>30</sup>

### Clinical characteristics

Hyperkplexia can present in the fetal life as abnormal intrauterine movements, or later at any time from neonatal period to adulthood.<sup>20–31</sup> The early manifestations include abnormal responses to unexpected auditory, visual, and somesthetic stimuli such as sustained tonic spasm, exaggerated startle response and fetal posture with flexion of forearm and legs, clenched fists, and anxious stare.<sup>3</sup> The tonic spasms may mimic generalised tonic seizures, leading to apnoea and death.<sup>32</sup> These spasms are not accompanied by epileptic discharges on electroencephalography (EEG).<sup>33</sup> Additional features are generalised hypertonia and prominent nocturnal/diurnal myoclonus with apnoea.<sup>2–34</sup> The hypertonia is apparent only when the infant is awake.<sup>7</sup> Consistent generalised flexor spasm in response to tapping of the nasal bridge (without habituation) is the clinical hallmark of hyperkplexia, though its mechanism is not very clear.<sup>7</sup> Though usually there is neither mental nor neurological deficiency, features of diffuse cerebral involvement with developmental delay are seen in some patients.<sup>35–36</sup> Umbilical, inguinal, and diaphragmatic hernias attributed to hypertonia are seen with increasing frequency in the affected infants.<sup>33</sup>

### Risk of SIDS

Sudden infant death syndrome (SIDS) is well reported in hyperkplexia.<sup>37–38</sup> Central apnoea related to brainstem dysfunction or peripheral apnoea after feeding difficulties with consequent aspiration and respiratory muscle spasm are the proposed mechanisms of SIDS.<sup>2–39</sup> Interestingly, the apnoeic episodes are known to disappear spontaneously by 2 years of age.<sup>8</sup> Sudden death may also be related to complete heart block and apnoea during the seizure-like episodes.<sup>32</sup>

### Evolution

Spontaneous amelioration of the hypertonia with increasing age and delayed gross motor development characterise the evolution of hyperkplexia.<sup>3</sup> Though the tone is usually almost normal by the age of 3 years, hypertonia may recur in adult life.<sup>40</sup> The exaggerated startle response, however, persists to adulthood leading to falls on the face or back without loss of consciousness.<sup>2</sup>

### Diagnosis

EEG is usually normal but may show fast spikes (myogenic origin) initially during the tonic spasms, followed by slowing of background activity with eventual flattening corresponding to the phase of apnoea bradycardia and cyanosis.<sup>7–35</sup> Electromyography shows a characteristic almost permanent muscular activity with periods of electrical quietness.<sup>33</sup> Electromyography can be used to monitor treatment and identify minor hyperkplexia.<sup>16</sup> Nerve conduction velocity is normal.<sup>33</sup> Proton magnetic resonance spectroscopic imaging

(MRSI) studies have shown reduced intensity of the neuronal marker *N*-acetylaspartate, choline containing compounds and creatinine in the frontal, central, and right frontal regions.<sup>12</sup> The topography of EEG abnormalities in the frontal lobes has coincided with MRSI findings in some patients. Whether such neuronal dysfunction represents cortical dysfunction or an epiphenomenon of diencephalic or brainstem abnormalities is currently unknown. No specific computed tomography findings have been reported yet.

### Differential diagnosis

The differential diagnoses of hyperkplexia in the neonatal period include the congenital stiff-man syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, and phenothiazine toxicity.<sup>40–41</sup> Hyperkplexia may also be misdiagnosed as cerebral palsy.<sup>7</sup> The differential diagnoses in adulthood includes neurological disorders with hypertonia like the Issacs Mertens syndrome,<sup>33</sup> the jumping Frenchman of Maine,<sup>42</sup> or somewhat similar clinical entities reported in different parts of the world (for example, miryachit in Siberia<sup>43</sup> and latah in Malaysia and Indonesia<sup>44</sup>), Gilles de la Tourette syndrome,<sup>33</sup> and Swartz Jampel syndrome.<sup>33</sup>

### Treatment

Clonazepam, a gamma aminobutyric acid (GABA) receptor agonist, is the treatment of choice for hypertonia and apnoeic episodes.<sup>45</sup> The degree of stiffness, however, may not be significantly influenced by clonazepam.<sup>46</sup> In contrast phenobarbitone, phenytoin, diazepam, and sodium valproate have not always consistently controlled the hypertonia and/or abnormal startle response.<sup>3</sup> A simple manoeuvre like forced flexion of the head and legs towards the trunk is known to be life saving when prolonged stiffness impedes respiration.<sup>47</sup>

### Conclusion

Recognition of hyperkplexia in the neonatal period is essential in avoiding erroneous diagnoses like epilepsy. Diagnosis should not be difficult, as consistent generalised flexor spasm in response to tapping of nasal bridge (without habituation) is the clinical hallmark. Though treatment of choice is clonazepam, a simple manoeuvre like forced flexion of the head and the legs towards the trunk can be life saving in presence of prolonged stiffness compromising respiration. Association with recurrent apnoeic spells, cardiac arrhythmia, SIDS, and severe feeding difficulties with apnoea indicates the need for providing home monitoring and appropriate parental counselling.

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