

## Hyperekplexia, A Rare Cause of Neonatal Hypertonia: Report of Two Cases

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Submitted: 28 Nov 2018; Accepted: 04 Dec 2018; Published: 21 Jan 2019

### Summary

*Hyperekplexia (startle disease) is a rare neurogenetic disorder, frequently misdiagnosed with the risk of choking on food, apnea and sudden death. Recognition of this disorder in the neonatal period is essential to avoid erroneous diagnoses and to start early treatment that has proven effective. We report two cases of two newborns who were initially admitted in our neonatal intensive care unit for management of suspected tetanus and epilepsy. Following clinical and paraclinical investigations, a final diagnosis of hyperekplexia was retained in both cases and a low dose of clonazepam was administered. The symptoms gradually decreased until disappearance of hypertonia and startles.*

**Keywords:** Hyperekplexia, newborn, neonatal hypertonia, startle disease.

### Introduction

Hyperekplexia or startle disease is a rare neurogenetic disease characterized by an exaggerated persistent startle reaction to unexpected auditory, somatosensory and visual stimuli associated to generalised muscular rigidity. It was first described by Kirstein and Silverskiold in 1958 [1]. The Greek name “Hyperexplexie” was given by Surhem in 1966 corrected in “Hyperekplexie” by Gastaut and Villeneuve a year later [2-3]. The disorder is also known as stiff baby syndrome [4]. It can be described as a glycine synaptopathy with known mutations residing in the major constituent parts of the inhibitory glycinergic system [5]. The expression of the disease is variable including minor forms that may be unnoticed and major forms with arthrogryposis-like symptoms, orthopedic complications, false passages, apnea and even sudden infant death (SID) hence the interest of early diagnosis [6]. Clonazepam has been the mainstay of treatment for this disorder to date [7]. We report two cases that responded well to this treatment in order to draw attention to this unusual clinical entity which is often misdiagnosed in neonates as congenital tetanus or a convulsive disorder.

### Cases presentation

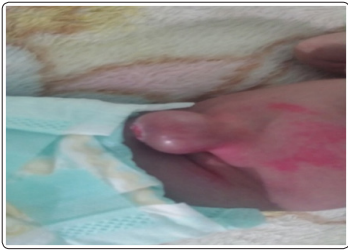
#### First case

A 23-days-old, male, first born to non consanguineous parents was admitted in our neonatal intensive care unit for management of suspected neonatal tetanus. The mother was 19-years-old. The pregnancy was not followed and there was no similar case in the family. He was a full term, 3 kg 100g home delivered baby who cried immediately following birth. He had presented since birth a generalized hypertonia with exaggerated startle reaction without feeding difficulties or cyanosis. Central nervous system

examination at admission showed generalized hypertonia without opisthotonos or trismus (Figure 1). Primitive reflexes were present with an exaggerated Moro reflex and a good sucking reflex. The anterior fontanel was flat and of normal size. Head circumference was normal. There were no dysmorphic features. We also noted an umbilical hernia (Figure 2). Other systemic examinations were not remarkable. Biological examinations requested as part of the infectious assessment (blood count, C-reactive protein and lumbar puncture) as well as the blood ionogram returned normal. Transfontanellar ultrasound was also normal. Electroencephalogram for newborn was not available in our unit during this period. During hospitalization we noticed that hypertonia and startle reaction decreased at sleep and increased with auditory and visual stimuli. The diagnosis of hyperekplexy has become so strongly suspected especially when we tried the “Vigevano Maneuver”, by forced flexion of the head and legs, which had effectively stopped the attack. Therefore, the newborn was placed on clonazepam at 0.1 mg/kg/day with gradual increase to 1 mg/day. Genetic counseling was done and the patient was referred to the pediatric surgeon for the management of umbilical hernia. The evolution was marked by the progressive regression until disappearance of hypertonia and a net decrease of the startles with a follow up of 2 years 6 months.



**Figure 1:** Generalized hypertonic attitude in the first newborn



**Figure 2:** umbilical hernia in the first newborn

### Second case

A 13-days-old, male, second born to non consanguineous parents was admitted for generalized hypertonia. The pregnancy was not followed estimated at 40 SA according to the score of FARR. He was vaginal delivered baby who cried immediately following birth. The infectious anamnesis was negative. He had presented since the birth a generalized hypertonia with episodes of generalized clonias without fever (figure 3). According to the mother, the stiffness decreased when the new born was asleep. There was no history of feeding difficulties or cyanosis. Also there was no family history of neurological disease. On CNS examination, rigidity was seen in all muscle groups including trunk and abdominal wall. Primitive reflexes were present. The patient held himself in a flexed posture, with anxious look. On tapping the nose an exaggerated startle response and a period of increased hypertonicity were demonstrated. The rest of the clinical examination was unremarkable. Initially, phenobarbital had been prescribed (20 mg/kg) due to a suspicion of neonatal seizures. However, the attack frequency remained the same. He was suspected to have infectious encephalitis or congenital tetanus. Biological examinations requested (blood count, C-reactive protein, lumbar puncture, and ionogram) were normal. Trans-fontanelar ultrasound was normal. EEG showed no epileptiform discharges. In light of the suggestive history and normal investigations a diagnosis of hyperekplexia was suspected especially in view of the positivity of the Vigevano maneuver, and clonazepam was administered to the patient at a low dose. A spectacular response was noted in the first days following the introduction of treatment with decreased tone and attenuation of startle reaction. Self-limiting course of the disease and its genetic mode of inheritance, with probability of the other siblings being affected, were explained to parents. After discharge from the hospital, the patient was seen several times. Hypertonia gradually decreased until its disappearance despite persistence of some startle reaction. The patient is currently 16 months old and regular assessment of psychomotor development did not show any abnormality.



**Figure 3:** Generalized hypertonia in the second newborn

### Discussion

Hyperekplexia is a rare non epileptic disorder the exact prevalence of which is unknown. This rare condition can present in the neonatal

period or early infancy, although late presentations have also been described [8]. It is characterized by two abnormal forms of response to unexpected auditory, visual and somesthetic stimuli, namely sustained tonic spasm (tonic extension of both upper and lower limbs or flexion of upper with extension of lower limbs) and the exaggerated startle response (which is a basic alerting reaction with stereotyped features consisting of eye blinking, facial grimacing, flexion of head, elevation of shoulders, and flexion of elbows, trunk and knees) [9]. Hyperekplexia is usually familial, most often autosomal dominant with variable expression [10]. Autosomal recessive form and sporadic cases have also been described [2]. Our cases represent “sporadic hyperekplexia,” as there was no positive family history. Hyperekplexia is related to mutations in genes affecting Glycinergic neurotransmission. Three major genes are known: Two genes code for the postsynaptic glycine inhibitor subunits: GLRA1 encoding the alpha1 subunit and GLRB encoding the beta subunits which are located on chromosome 5q33-35 [2,3,5,7]. There is also a third gene: SLC6A5, which encodes the glycerine-related presynaptic glycerin transporter (GlyT2), which is thought to be responsible for some forms of hyperekplexie [11]. The lack of mutual inhibition at the medullary level could explain the generalized hypertonia. Inhibitory glycinergic synapses are located predominantly in the spinal cord and brainstem and disruptions to their function increase the general level of excitability of motor neurons, thus accounting for neonatal hypertonia [12]. Hyperekplexy is characterized in its congenital and major form by hypertonia, hypokinesia and especially by significant hyperexcitability, which appear in the first hours of life, with the occurrence of exaggerated startle response to unexpected tactile or auditory stimulus [6, 13]. Additional features include generalized hypertonia decreasing with sleep with hypokinesia, nocturnal myoclonus, increased incidence of congenitally dislocated hips, feeding difficulties with increased incidence of difficult labor and abnormal intrauterine movements [14]. Inguinal or diaphragmatic hernias have been described in some patients, explained by the exaggerated and recurrent contraction of the abdominal musculature [15]. An umbilical hernia was noted in our first case. Consistent generalized flexor spasm in response to tapping of the nasal bridge (without habituation) is the clinical hallmark of hyperekplexia, though its mechanism is not very clear. “Vigevano” maneuver, which consist of forced flexion of the head and legs toward the trunk may relieve attacks, especially in the newborn period. This maneuver allowed stopping the attack in our two cases and it was a good argument for the diagnosis of hyperekplexia. The Deep tendon reflexes are normal and there is no sign of pyramidal irritation. Complementary biological examinations and brain imaging are normal as is the case in our patients [13]. Electromyography can aid diagnosis by revealing characteristic sustained myogenic activity [10, 11, 15, 16]. It would be especially useful for detecting minor forms and for verifying therapeutic efficacy. Molecular diagnosis can be done but is not available in Morocco. Risk of death from apnea caused by severe spasms has been documented in hyperekplexia. The alimentation may also represent a somesthetic stimulus that may cause or pharyngeal in coordination with risk of pulmonary inhalation and apnea [17]. Rigidity decreases significantly after the first year of life and disappears around 3 years. However, in some cases mild stiffness reappears in adolescence or adult life and spasms may again be provoked by startle [18]. Such episodes are a source of injury. Delayed motor milestones are present while cognitive function normally remains unaffected, though low intelligence has been noted in some studies [19]. Differential diagnoses of hyperekplexia are mainly represented by

epilepsy, neonatal tetanus and symptomatic forms of anoxo-ischemic encephalopathies, infectious encephalitis and brain stem lesions [16]. Our first patient was initially addressed in our unit for management of suspected neonatal tetanus and the second one for suspected epilepsy. The diagnosis of hyperekplexia was retained in both cases only after eliminating differential diagnoses. Hyperekplexia is also distinguishable from certain syndromic entities such as Swartz-Jampell syndrome [20]. Clonazepam, a gamma aminobutyric acid (GABA) receptor agonist, is the treatment of choice for reducing hypertonia and preventing apnea in hyperekplexia [7]. A dose of 1 mg / kg / day has proven effective in a double-blind, placebo-controlled study. In children, lower doses are needed [6]. A dose lower than 1 mg / kg / day was sufficient in our both patients. Other drugs such as phenobarbital, phenytoin, diazepam and sodium valproate have shown no efficacy. One case treated with levetiracetam after failure of treatment with clonazepam has been reported [8].

### Conclusion

Recognition of hyperekplexia 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. Treatment of choice is clonazepam and a simple maneuver by forced flexion of the head and the legs towards the trunk can be life saving in presence of prolonged stiffness compromising respiration.

### Declaration of conflicts of interest

The authors declare that they have no conflicts of interest.

### Funding sources

Self financing by the authors

### Contributions of the authors

All authors contributed to this work, read and approved the final manuscript

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