Startle disease–two sibling cases

Mürüvet Elkay[1], Faruk İncecik[2], M. Özlem Hergüner[1], Göksel Leblebisatan[1]
Şakir Altunbaşak[1]

[1]Department of Pediatric Neurology, Çukurova University Faculty of Medicine, Adana, and [2]Department of Pediatrics, Mustafa Kemal University Faculty of Medicine, Antakya, Turkey

SUMMARY: Elkay M, İncecik F, Hergüner MÖ, Leblebisatan G, Altunbaşak Ş. Startle disease-two sibling cases. Turk J Pediatr 2005; 47: 275-278.

Startle disease (hyperekplexia) is a rare non-epileptic disorder characterized by hypertonia, generalized stiffness and brief muscle jerks in response to unexpected auditory, somatosensory and visual stimuli.

In this paper, two siblings with generalized stiffness and sudden muscle jerks to unexpected stimuli of various types are presented. They were previously misdiagnosed as epilepsy and treated with the conventional antiepileptic drugs. We wanted to call attention to and increase awareness of this rare disease and its differential diagnosis to avoid unnecessary investigations and treatment.

Key words: startle, hyperekplexia, differential diagnosis.

Startle disease, also known as hyperekplexia, is a rare non-epileptic disease. It is characterized by an exaggerated persistent startle reaction to unexpected auditory, visual and somatosensorial stimuli, generalized muscle stiffness, nocturnal myoclonus, and generalized hyperreflexia. It usually presents in the neonatal period with sustained tonic spasms, exaggerated startle reaction, fetal posture with clenched fists and anxious stare. The tonic spasms may mimic generalized tonic seizures and, seldomly, may cause apnea and death[1].

It is often passed through autosomal dominant inheritance with variable penetrance, but recessively inherited and sporadic forms of the disease are also seen. Hypertonia decreases within a few months and disappears by two to three years of age, while the exaggerated startle response may persist up to adulthood[2,3].

Delay in the diagnosis may lead to unnecessary investigations and inappropriate treatment. In this paper, two siblings with startle disease are presented to call attention to this disease and its differential diagnosis.

Case Reports

Case 1

A five-month-old infant was brought to our clinic by his parents with the complaints of sudden muscle jerks and diffuse muscle stiffness accompanied by cyanosis in response to unexpected auditory, visual and somatosensorial stimuli. He was born by normal delivery to second-degree consanguineous parents. Psychomotor development was normal. His parents stated that he had experienced these episodes since the 2nd or 3rd day of life. He was diagnosed as epilepsy and was given phenobarbital (PB) two months previously, but showed no improvement. Family history revealed only one affected member: his brother (Fig.1).

In physical examination, vital signs were normal. Length, weight and head circumference were also normal. In neurological examination, the muscle tone was increased and deep tendon reflexes (DTRs) were brisk. On lightly tapping of the bridge of the nose with a finger, there was an exaggerated startle response with symmetrical myoclonic jerking of limbs. The remainder of the physical and neurological examinations was unremarkable.

Laboratory examinations including complete blood count, blood biochemistry, lactic and pyruvic acids, urine and blood amino acids were normal. Electrocardiography (ECG), cerebral computed tomography (CT), and electroencephalography (EEG) were also normal.

He was also followed up in our clinic with the diagnosis of epilepsy for a while. At first, PB was tapered slowly and valproic acid (VPA)

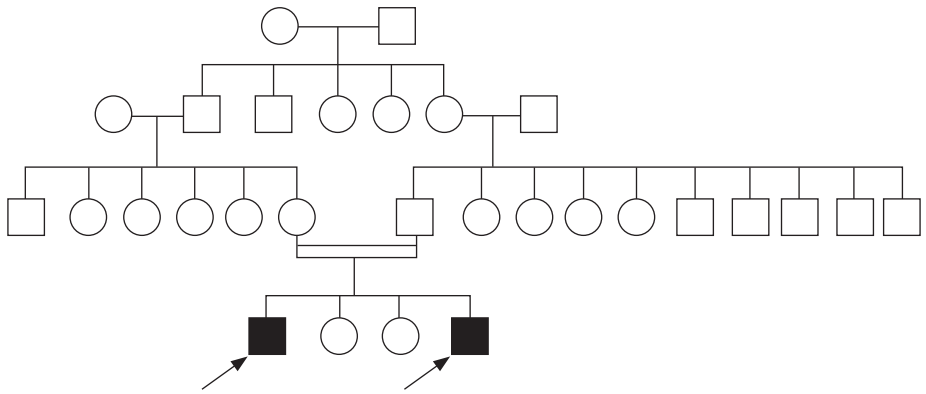

Fig. 1. Pedigre: the affected members are indicated by filled symbols; unaffected members by open symbols.

was started (10 mg/kg/day, in two divided doses). At seven months, his parents informed us that he showed no improvement. VPA was increased to 30 mg/kg/day. There continued to be no improvement at nine months. Because of the treatment failure, he was reevaluated and diagnosed as startle disease. VPA was tapered slowly, and clonazepam was started (0.03 mg/kg/day, in two divided doses). After one week, there was a marked decrease in his complaints. At 11 months, clonazepam was increased to 0.07 mg/kg/day. At the last follow-up visit, he was 1.5 years old. Psychomotor development was normal. In neurological examination, the muscle tone was increased and DTRs were brisk. On nose tapping, there was a uniform reaction of facial twitching accompanied by head extension. Clonazepam treatment was continuing.

Case 2

An eight-year-old male, the brother of the first case, was brought to our clinic by his parents because of similar complaints since birth. Additionally, he would fall to the ground in response to unexpected stimuli and had suffered severe facial lacerations and concussions as a result.

Past history was unremarkable. He had been placed on PB and VPA treatment consecutively but did not show any improvement. When he was admitted to our clinic, he was still taking VPA (40 mg/kg/day, in two divided doses).

Physical and neurological examinations were normal, except increased DTRs and positive nose tapping test. Complete blood count, blood biochemistry, serum lactic acid/pyruvic acid, urine and blood aminoacids, ECG, cerebral CT, and EEG were normal.

He was diagnosed as startle disease and given clonazepam. VPA was tapered slowly. After three months, there was a significant decrease in his complaints. He continues to be followed in our clinic. At the last follow-up visit, he was nine years old. He had experienced no new falls to the ground in response to unexpected stimuli. In neurological examination, there were increased DTRs and positive nose tapping test. He was still using clonazepam.

Discussion

Startle disease, or hyperekplexia, one of the childhood non-epileptic paroxysmal disorders, was first reported in 1966 by Suhren et al[4]. The disease is rare and the prevalence remains unknown. It has two distinct clinical forms: minor and major. The minor form is characterized by excessive startle response which occurs in infancy by febrile illness and in adult life by emotional stress. The major form is seen in newborns shortly after birth and is characterized by hypertonia, hyperreflexia, and exaggerated startle response to unexpected stimuli.

The startle reaction can be elicited by nose tapping which causes sudden head retraction, symmetrical myoclonic jerking of limbs, or tonic flexion of body[5]. The tactile stimuli during feeding in newborns and infants can cause apnea or aspiration pneumonia and consequently sudden infant death by inducing oropharyngeal incoordination and poor air exchange. Untreated children suffer severe injuries from frequent falls with exaggerated startle response. They usually have insecure gait due to fear of falling[6]. Our cases were considered as major form of the disease regarding the onset and clinical findings.

The hypertonicity and hyperreflexia diminish spontaneously after the first year of life and usually disappear by the end of three years of age, while exaggerated startle response often persists into adult life[7]. The hypertonicity may cause delay in the acquisition of early motor milestones but catch-up occurs as the hypertonia diminishes. Rarely, mild mental retardation can be seen[7]. In our cases, psychomotor development was normal. The second case continued to have exaggerated startle response and frequent falls until he was given appropriate treatment at the age of eight years.

Startle disease is usually familial but sporadic cases may also be seen. In familial cases, it is often inherited autosomal dominantly, and the defective gene is located at the long arm of chromosome 5 (5q33-35)[8]. It encodes the α1 subunit of the inhibitory glycine receptor (GLRA1). It is a ligand-gated chloride channel provoking postsynaptic hyperpolarization which mediates synaptic inhibition in the brainstem and spinal cord. Several missense mutations of the GLRA1 gene have been identified in families with autosomal dominant hyperekplexia. Different mutations in the GLRA1 gene have been reported in cases with autosomal recessive hyperekplexia[9]. Most sporadic cases do not have mutations in the GLRA1 gene. By examining the pedigree, we could say that our cases appeared to be familial, as indicated by the affected sibling pairs and a history of consanguineous parentage. We were able to determine the inheritance pattern only by genetic studies in this noninformative family.

The pathophysiology underlying startle disease has not been established yet. However, the findings of extensive electrophysiological studies performed in patients and in the mouse models strongly support that the primary physiological abnormality is increased excitability in pontomedullary reticular neurons and abnormal spinal reciprocal inhibition[10]. Shiang et al.[8] claimed that a point mutation at the long arm of chromosome 5 encoded the defective α1 subunit of the inhibitory glycine receptor, which caused a decrease in inhibitory neurotransmission and hyperekplexia. Rees et al.[11] detected a mutation in the β subunit of the inhibitory glycine receptor (GLRB) in rats, and he speculated that mutations in the GLRB gene might contribute to some cases of startle disease with no detectable mutations in the GLRA1 gene. Dubowitz et al.[12] demonstrated that there was a low gamma-aminobutyric acid (GABA) level in patients with startle disease. He concluded that this might be responsible for the hyperexcitability.

Startle disease is often misdiagnosed as epilepsy because the patients with startle disease can manifest startle reactions, such as symmetrical myoclonic jerking of limbs or tonic flexion of the body in response to unexpected stimuli. These reactions may be confused with myoclonic epileptic syndromes and generalized tonic convulsions[13]. The possibility of epilepsy is excluded as the episodes are state-related, can be induced, and EEG does not show any abnormalities. If the diagnosis is not made appropriately, some patients with startle disease may be treated by antiepileptics unproperly, and get no benefit[14]. Our cases were misdiagnosed as epilepsy and treated by conventional antiepileptic drugs.

Perinatal asphyxia, sepsis, central nervous system hemorrhage or malformations should also be considered because hypertonicity and irritability can be seen in these conditions[7,12]. In our cases, they were ruled out by the history and neuroimaging study. Other non-epileptic disorders like benign neonatal sleep myoclonus and neonatal tetanus should be kept in mind while making differential diagnosis. In benign neonatal sleep myoclonus, myoclonia occurs only in sleep, while in startle disease, contractions can occur both in sleep and in awake state[15]. Our cases had myoclonia while both asleep and awake. In the diagnosis of neonatal tetanus, the presence of unhygienic child birth practices, social taboos, or improper immunization of pregnant mothers is imperative. Also, the clinical findings in neonatal tetanus, such as rigidity, failure to suck, trismus, fever, and seizures make differential diagnosis easy[16,17]. The exaggerated startle response may be easily differentiated from the exaggerated Moro's response seen in spastic quadriplegia and the pathologic startle seen in Tay-Sachs disease[7].

McAbee et al.[18] reported an infant with sporadic startle disease in whom tonic spasms were accompanied by complete heart block and apnea, and he concluded that these findings could be related to sudden infant death in

startle disease. We monitored the first case and obtained a short ECG recording in the second case. Both were normal.

EEG findings in startle disease differ from one study to another. The paroxysmal activities like bilateral, synchronized, and symmetrical sharp and spike waves were detected at the frontocentral localization in one study[13], but these activities were evaluated as artifacts arising from the movements of eyes or muscles in the other[19]. Nigro et al.[20] found that EEG was normal in 15 patients with startle disease. EEGs of our cases were also normal.

The hypertonia and hyperreflexia diminish with time and usually disappear by the age of three, while exaggerated startle response often persists into adult life. The treatment of startle disease is easy. Clonazepam is the drug of choice, which decreases exaggerated startle response and consequently reduces the morbidities and mortalities of the disease. It is a GABA receptor agonist, potentiating GABA-gated chloride channel function and compensating for the defective glycine-gated chloride channel function in startle disease[7,10]. Valproic acid, clobazam, piracetam, vigabatrin, and lamotrigine have been used with some success[7,21,22]. Even though there are no definite guidelines regarding duration of therapy, the drug can be tapered slowly once the symptoms abate[7,23]. Our cases were given clonazepam and they showed marked improvement. If a baby has a tonic episode in sleep, cardiopulmonary arrest can occur and this may be halted by sudden flexion of the head and neck. This procedure should be recommended to parents for application during prolonged attacks[19].

In conclusion, startle disease is a rare but treatable neurogenetic disease. By increasing awareness of the disease, it can be diagnosed easily and this will lead to appropriate treatment and genetic counseling.

REFERENCES

1. Praveen V, Patole SK, Whitehall JS. Hyperekplexia in neonates. Postgrad Med J 2001; 77: 570-572.
2. Gordon N. Startle disease or hyperekplexia. Dev Med Child Neurol 1993; 35: 1015-1018.
3. Tohier C, Roze JC, David A, et al. Hyperekplexia or stiff-baby syndrome. Arch Dis Child 1991; 66: 460-461.
4. Suhren O, Bruyn GW, Tuynman JA. Hyperekplexia. A hereditary startle syndrome. J Neurol Sci 1966; 3: 577-605.
5. Shahar E, Brand N, Uziel Y, et al. Nose tapping test inducing a generalized flexor spasm: a hallmark of hyperexplexia. Acta Paediatr Scand 1991; 80: 1073-1077.
6. Tijssen MA, Vergouwe MN, van Dijk JG, et al. Major and minor form of hereditary hyperekplexia. Mov Disord 2002; 17: 826-830.
7. Rajadhyaksha SB, Bahl VB. Hyperekplexia: a non-epileptic startle disorder. Indian Pediatr 2002; 39: 773-776.
8. Shiang R, Ryan SG, Zhu YZ. et al. Mutation in the alpha-1 subunit of the inhibitory glycine receptor causes the dominant neurologic disorder, hyperekplexia. Nat Genet 1993; 5: 351-358.
9. Rees MI, Andrew M, Jawad S, Owen MJ. Evidence for recessive as well as dominant forms of startle disease (hyperekplexia) caused by mutations in the alpha 1 subunit of the inhibitory glycine receptor. Hum Mol Genet 1994; 3: 2175-2179.
10. Zhou L, Chillag KL, Nigro MA. Hyperekplexia: a treatable neurogenetic disease. Brain Dev 2002; 24: 669-674.
11. Rees MI, Lewis TM, Kwok JB, et al. Hyperekplexia associated with compound heterozygote mutations in the beta-subunit of the human inhibitory glycine receptor (GLRB). Hum Mol Genet 2002; 11: 853-860.
12. Dubowitz LM, Bouza H, Hird MF, et al. Low cerebrospinal fluid concentration of free gamma aminobutyric acid in startle disease. Lancet 1992; 340: 80-81.
13. Fejerman N. Myoclonus and epilepsies. Indian J Pediatr 1997; 64: 583-602.
14. Andermann F, Keene DL, Andermann E, et al. Startle disease or hyperekplexia: further delineation of the syndrome. Brain 1980; 103: 985-997.
15. Egger J, Grossmann G, Auchterlonie IA. Benign sleep myoclonus in infancy mistaken for epilepsy. BMJ 2003; 326: 975-976.
16. Yaramiş A, Tas MA. Neonatal tetanus in the southeast of Turkey: risk factors, and clinical and prognostic aspects. Review of 73 cases, 1990-1999. Turk J Pediatr 2000; 42: 272-274.
17. Bhatia R, Prabhakar S, Grover VK. Tetanus. Neurol India 2002; 50: 398-407.
18. McAbee GN, Kadakia SK, Sisley KC, et al. Complete heart block in non-familial hyperekplexia. Pediatr Neurol 1995; 12: 149-151.
19. Pascotto A, Coppola G. Neonatal hyperekplexia: a case report. Epilepsia 1992; 33: 817-820.
20. Nigro MA, Lim HC. Hyperekplexia and sudden neonatal death. Pediatr Neurol 1992; 8: 221-225.
21. Stephenson JB. Vigabatrin for startle-disease with altered cerebrospinal-fluid free gamma-aminobutyric acid. Lancet 1992; 340: 430-431.
22. Stewart WA, Wood EP, Gordon KE, et al Successful treatment of severe infantile hyperekplexia with low-dose clobazam. Child Neurol 2002; 17: 154-156.
23. Narchi H. Index of suspicion. Case 2. Hyperekplexia. Pediatr Rev 2000; 21: 175-176.