Brain & Development 39 (2017) 306–311

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Hyperekplexia: Report on phenotype and genotype of 16 Jordanian patients

Amira Masri [a,*], Seo-Kyung Chung [b], Mark I. Rees [b]

[a] Faculty of Medicine, The University of Jordan, P.O. Box 1612 Code, 11941 Amman, Jordan
[b] Institute of Life Sciences, Swansea University Medical School, Swansea University, UK

Received 28 July 2016; received in revised form 15 October 2016; accepted 20 October 2016

Abstract

Background: Hyperekplexia, is a rare disorder characterized by excessive startle response to acoustic, visual, or other stimuli. It is inherited in autosomal recessive and dominant pattern.

Objective: To describe the clinical and genetic features of hyperekplexia in Jordanian patients.

Methods: This retrospective study includes all patients with proved genetic diagnosis of hyperekplexia who presented to our clinic at the Jordan University Hospital from January 2001 through July 2015.

Results: A total of 16 children from 12 families were included. The total follow up period ranged from one to eleven years. The majority of the patients (13/16 = 81.3%) were initially misdiagnosed as epilepsy.

All patients had excessive startle response since birth. Tonic–apneic spells occurred in 15/16 = 93.8% patients. Fourteen patients (45/16 = 87.5%) received clonazepam. Stopping clonazepam by three years of age failed in 11/14 (78.6%) due to reappearance of tonic–apneic spells (8/14 = 57.1%), recurrent falling (10/14 = 71.4%) or due to both reasons (5/14 = 35.7%).

Delayed motor development occurred in 7/16 (43.8%), speech delay in 4/16 (25.0%), global developmental delay in 1/16 (6.3%), and autism spectrum disorder in 1/16 (6.3%) patient. The mode of inheritance is autosomal recessive in all 12/12 (100%) families.

Mutations in *GLRA1* gene was present in 9/16 (56.3%); the most common mutation was in p.G254D (4/9; 44.5%). Mutations in the *GLRB* gene was present in 4/16 (25.0%) patients and the *SLC6A5* gene in 3/16 (18.8%) patients.

Conclusion: The clinical presentation of hyperekplexia in Jordanian patients is manifested by tonic–apneic spells in all homozygous patients. The persistence of apneic spells and recurrent falls throughout childhood necessitate continuous treatment and surveillance.

Keywords: Hyperekplexia; Misdiagnosis; Apnea; Nose tap; Consanguinity; Jordan

1. Introduction

Hyperekplexia, also known as hereditary startle disease, is a rare disorder characterized by excessive startle response to acoustic, visual, or other stimuli and hypertonia which predominates in the trunk and the lower limbs [1,2].

The disease can present in fetal life as abnormal intrauterine movements, or later at any time from the neonatal period to adulthood [3]. Manifestations in the neonatal period include tonic non epileptic seizures that are characteristically not accompanied by EEG abnormality and abnormal startle response to auditory,

* Corresponding author.
E-mail addresses: masriamira69@hotmail.com (A. Masri), s.chung@swansea.ac.uk (S.-K. Chung), m.i.rees@swansea.ac.uk (M.I. Rees).

http://dx.doi.org/10.1016/j.braindev.2016.10.010

visual, or somesthetic stimuli [4]. Tapping or touching the nose elicits sudden head retraction, a dramatic head recoil, and body tonic flexion; a characteristic feature of hyperekplexia [5].

Hyperekplexia was initially misrepresented as demonstrating solely autosomal dominant inheritance, however, recent literature reports that autosomal recessive inheritance is the major mode of inheritance with autosomal dominant cases contributing to only 16% of the cases [6].

Damaging mutations in several inhibitory glycinergic genes result in classical hyperekplexia. These include mutations in the genes encoding the postsynaptic inhibitory glycine receptor (hGlyR; *GLRA1&GLRB*) and the presynaptic glycine transport (GlyT2; *SLC6A5*) genes [7–10].

The clinical features of some hyperekplexia patients were previously-reported in Jordanian families [11]. In this study we report more on the clinical features and follow up in addition to the genetic findings of hyperekplexia in sixteen Jordanian patients from 11 consanguineous families and one non consanguineous family.

2. Methods

This retrospective study included all patients diagnosed with hyperekplexia at our child neurology clinic at Jordan University Hospital from January 2001 through July 2015. For the purpose of this study only patients with hyperekplexia who underwent genetic analysis with a gene-positive outcome were included. Files were reviewed to collect data regarding the clinical picture and genetic findings.

This study was approved by the scientific committee of the University of Jordan.

3. Results

A total of 16 children from 12 families were included; 11 boys and 5 girls (ratio of 2.2:1). The total follow-up period in our clinic ranged from one to eleven years (average 5.5 years). Most of the patients (13/16 = 81.3%) were initially misdiagnosed as epilepsy before referral to our center. All patients underwent EEG and none of them had any interictal or ictal abnormality. Furthermore, it was not easy at the beginning to convince the parents that their child has hereditary hyperekplexia and many parents continued to refer to their child's condition as epilepsy. In one patient symptoms were erroneously attributed to an associated gastro-esophageal reflux and a hiatus hernia. Age at correct diagnosis ranged from one month-21 years including ⩽one year in 10/16 (62.5%), 1–6 years in 4/16 (25.0%) and >6 years in 2/16 (12.5%).

3.1. Clinical features

3.1.1. Excessive startle and positive nose tap

All patients had excessive startle response since birth. Furthermore, in 7/16 (43.8%) of patients, the mothers experienced abnormal intrauterine jitteriness.

All patients had positive nose tap response.

3.1.2. Tonic–apneic spells

Almost all the patients (15/16 = 93.8%) had tonic–apneic spells except one patient who manifested a heterozygous inheritance and his clinical presentation was mainly excessive startle response and 'falling like a statue' upon sudden external stimulation. The age of onset of tonic–apneic spells was in the first week of life in most of the patients (13/16 = 81.6%), only two patients (2/16 = 12.5%) had delayed onset to two weeks and six months.

Furthermore, all patients had muscle stiffness during the early months of life

3.1.2.1. Response to treatment and follow up. Fourteen patients (14/16 = 87.5%) received clonazepam which controlled the tonic–apneic spells in all of them. Two patients (2/16 = 12.5%) did not need treatment because of absence of tonic–apneic spells upon presentation to us. Two patients developed excessive sleepiness and hypotonia as a side-effect of clonazepam which necessitated decreasing the clonazepam dose and addition of Phenobarbital to control the spells. Dose adjustment according to weight to control the tonic–apneic spells was needed mainly in the first year of life. The practice in our clinic is to start clonazepam with a dose of 0.1 mg/kg/day and to increase the dose gradually until tonic–apneic spells disappear, then to try to stop clonazepam at two years of age. We succeeded to stop treatment in only 3/14 (21.4%) patients at 10 months (stopped by parents), two years and three years. In the remaining patients, stopping clonazepam failed because of the reappearance of tonic–apneic spells (8/14 = 57.1%) or due to unsteady gait and recurrent startle-induced falls (10/14 = 71.4%) or due to both reasons (5/14 = 35.7%). However, very low doses of clonazepam (0.2 mg–1.0 mg/day) were needed to control the symptoms after two years of age in the majority of patients (Table 1). Dose adjustment of clonazepam was based upon the patients' clinical response.

3.1.2.2. Development and educational performance. Delayed motor development occurred in 7/16 patients (43.8%) with the age of walking in this group ranging from 18 months to 2.5 years. Speech delay was reported in 4/16 (25.0%) patients in the first years of life but all recovered from this delay. Global developmental delay was observed in1/16 (6.3%) patient and autism spectrum disorder in another patient1/16 (6.3%). Intelligent