The startle reflex in children with neuropsychiatric disorders

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Clonazepam is an effective treatment for hyperekplexia due to a SLC6A5 (GlyT2) mutation

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Abstract

A SLC6A5 (GLYT2) mutation hyperekplexia case is described with electrophysiological and psychiatric details before and during treatment with clonazepam. Not only the excessive startle reflex diminished, but also the anxiety symptoms clearly decreased during treatment. This is the first report of an electrophysiologically confirmed therapeutic effect of clonazepam in an hyperekplexia patient with a mutation in the SLC6A5 gene.
Introduction

The hyperekplexia ‘major’ form phenotype is a disorder characterized by continuous generalized stiffness during the first years of life, lifelong excessive startle reflexes followed by a short-lasting generalized stiffness and often an exaggerated head-retraction reflex.251 The disorder is associated with mutations in the GLRA1 gene (GLRA1) on chromosome 5q33-35.251 However, a recent report described a second important gene, the GLYT2 gene (SLC6A5), to cause the hyperekplexia phenotype.318 In patients with GLRA1 mutations clonazepam was found to effectively reduce startle reflexes.251 However, in patients with SLC6A5 mutations clonazepam was only described to be clinically effective in three out of five patients.318 We describe the effect of clonazepam in a genetically confirmed SLC6A5 mutation hyperekplexia ‘major’ form patient (case number 5318) with electrophysiological and psychiatric assessments before and during treatment.

Clinical description

The patient (Turkish, male, consanguineous parents) suffered from excessive startle reflexes all his life. As a neonate he experienced episodes with apnoea and had trouble swallowing. Incidentally he suffered from generalized tonic clonic seizures. Electroencephalography showed bilateral synchronous epileptic activity and he was treated with phenobarbital. The following 7 electroencephalograms during his first year of life were all normal and the phenobarbital was discontinued. At neurological examination at the age of 1.5 years, the head-retraction reflex and a subtle general stiffness were present. The patient showed an extensor plantar response on the left side. Because no GLRA1 mutation was detected, the patient was diagnosed with symptomatic excessive startle reflexes. As parents did not approve medication, the patient was not treated with clonazepam. At the age of 3.5 years the patient could walk, but frequently fell forwards ‘as stiff as a stick’, and suffered multiple clavicula fractures and facial bruises. At the age of 6 years the patient was able to bend his knees during the falls and slide down to the floor. At the age of 8 years genetic analysis revealed an homozygous single missense mutation (C1274T) in the SLC6A5.318 At this age the patient developed considerable anxiety related to his excessive startle reflexes. He did not ride a bike, climb the stairs, run nor participate with gymnastics. During walking, falling could be reduced in frequency by holding something like keys or a coat. Additionally, his parents reported nocturnal myoclonus.
Measurements

Baseline
Responses following binaural auditory stimulation by headphones (104 dB SPL, 50 ms, 2000 Hz pure tones with instantaneous rise and fall times) presented to the patient every 1.5 to 2.5 minutes were measured with an electromyogram (EMG) in the orbicularis oculi, sternocleidomastoid, masseter, deltoid, abductor pollicis brevis and quadriceps muscles. The averaged (n=8) EMG auditory startle reflex (ASR) was compared to a an age and sex matched control (a healthy 9 year old boy)(Figure 1). The startle reflex of the patients was clearly enlarged. Psychiatric assessment showed that the patient met criteria for DSM-IV diagnoses of social phobia, generalized anxiety disorder and height phobia. Psychiatric questionnaires showed that general anxiety symptoms were in the clinical range (score child report 18, score parent report 28). Behavioral problems reported by parents showed major internalizing symptoms (i.e. anxiety and affective problems) of the patient (score 65; in the 93th percentile). Clonazepam (1 mg dd) was started after the EMG recordings.

Follow up
At follow up, three months after the initiation of clonazepam, a reduced number of startle-induced falls and notably less impairment by his symptoms were reported by the parents. The patient now played outside, practised karate, rode his bike and walked alone to school. The ASR of the patient and the matched control was assessed again. In the patient the magnitude of the EMG signal at follow up was clearly reduced compared to baseline (Figure 1). The EMG activity of the control subject was comparable to his activity during the initial registration (Figure 1). At follow up the anxiety disorders in the patient were still present. However, the psychiatric questionnaires revealed that general anxiety symptoms were reduced by 45 % as reported by the patient (child score 8) and by 31 % as reported by the parents (parent score 18). Internalizing symptoms were reduced by 28 percentiles (score 54; in the 65th percentile). The anxiety disorders were considered in remission after another six months.

Significance and recommendations
Here, we describe for the first time the effect of clonazepam on the clinical symptoms, the electrophysiologically assessed startle reflex and the typical comorbid anxiety symptoms of a patient with a SLC6A5 mutation. Not only the excessive startle reflex diminished, but also the anxiety symptoms clearly decreased during treatment with

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1 In addition, in chapter 3 it was described that in a group of 27 children there was no effect of this time period (12 weeks) on their similarly assessed ASR.
Clonazepam has anxiolytic properties, but the improvement of the anxiety symptoms are most likely related to the reduced number of startle-induced falls and the major reduction of the startle reflex. This study confirms that clonazepam can be effective in SLC6A5 positive patients. As such screening of the second hyperekplexia gene $\textit{SLC6A5}$ should be considered in patients with the hyperekplexia 'major' form phenotype\textsuperscript{251} without a $\textit{GLRA1}$ mutation.

**Figure 1.** Averaged EMG of eight ASRs elicited by 104 dB tones at baseline (A) and follow up (B) of patient with SLC6A5 mutation and matched control. OO = orbicularis oculi, MA = masseter, SC = sternocleidomastoid, DE = deltoïd, AP = abductor pollicis brevis, QU = quadriceps. Black line: Patient (A) before treatment clonazepam, (B) during treatment clonazepam three months later. Grey line: Matched control, (A) baseline (B) follow up 3 months later.