SciMedCentral

Journal of Autism and Epilepsy

Case Report

Epileptiform Discharges in a Patient with Angelman Syndrome

Maria Arvio[1]*, Timo Nyrke[1], Markus Müller[2], and Nina Bjelogrlic-Laakso[3]

[1]*PEDEGO Research Unit, Oulu University Hospital, Finland*
[2]*Center for Integrated Protein Science (CiPSM) at the Department of Chemistry, Turku University Hospital, Germany*
[3]*Department of Intellectual Disability Medicine, Tampere University Hospital, Finland*

***Corresponding author**
Maria Arvio, Joint Authority for Päijät-Häme Social and Health Care, Lahti; PEDEGO Research Unit, Oulu University Hospital; Southwest Special Care Municipal Authority, Paimio, Finland, Tel: 358400835614; Email: maria.arvio@phsotey.fi

Submitted: 24 May 2017

Accepted: 13 June 2017

Published: 17 June 2017

Keywords
- Angelman syndrome
- Myoclonic status in non-progressive syndrome (MSNPS)
- Stiripentol

Abstract

In this paper, we describe a 42-year old woman with intellectual disability of unknown origin, epilepsy and treatment resistant neuropsychiatric symptoms, who was bed-ridden for decades until the identification of the underlying genetic syndrome, Angelman syndrome, as well as the recognition of the specific epilepsy syndrome, myoclonic status in non-progressive syndrome, and the initiation of an orphan antiepileptic drug, stiripentol, with good response.

INTRODUCTION

Angelman syndrome (AS) is a genetically determined rare disorder. It is caused most often by a deletion on chromosome 15q11-13 (70-75%), or by a uniparental disomy, an imprinting defect, or UBE3A mutation. Conventionally, AS is characterized by severe/profound intellectual disability (ID), epileptic seizures, sleep disturbance, jerky movements and frequent laughter [1]. On the other hand, AS occasionally associates with another even more rare disorder, myoclonic status in non-progressive syndrome (MSNPS) [2,3].

Epilepsy in patients with ID may be under diagnosed due to several factors [4]. Firstly, clinicians may not recognize the underlying epileptic seizures simply because of the rarity of these cases. Secondly, even epilepsy specialists can easily misinterpret atypical epileptic seizures as movement disorders (related to the underlying syndrome) instead of recognizing those as epileptic signs. Thirdly, numerous confounding factors such as the natural course of the ID syndrome, often highly variable signs of the associated comorbidities and also adverse reactions related to the pharmacotherapy may complicate the diagnostics. Furthermore, these patients cannot usually express themselves of their symptoms making e.g. the identification of side effects difficult. In addition, the much needed diagnostic procedures e.g. brain imaging and video-EEG, may remain undone because of problems in compliance and co-operation.

MSNPS is a good example of an epilepsy syndrome with highly variable signs [3]. In the medical literature, it is characterized as status epilepticus of myoclonic jerks and sub-continuous absences. The symptoms such as myoclonic jerks involving eyelids, face, and limbs are described as mostly erratic and asynchronous, becoming more rhythmic and synchronous during the absences. Patients with MSNPS are known to have also other types of seizures but almost never tonic seizures. In addition, MSNPS can manifest as sudden spontaneous massive startle attacks and abrupt loss of postural tone as well as long-lasting bursts of intentional myoclonus or tremor.

Nowadays modern imaging and molecule-genetic methods are applied commonly in children with developmental delay, but such information is still lacking for many adults with ID. In this paper, we describe a 42-year old woman with ID of unknown origin, epilepsy and treatment resistant neuropsychiatric symptoms, who was bed-ridden until the identification of the underlying genetic ID syndrome as well as the recognition of the specific epilepsy syndrome and the initiation of an orphan antiepileptic drug (AED) with good response.

Guardian of the patient has given a written permission for publishing this case report.

CASE REPORT

The patient is a 42-year old woman. At the age of five, she had been diagnosed to have an autism spectrum disorder, severe ID, pes planus, ataxia and epilepsy of unknown cause. She learned to crawl but not to speak. She communicated with gestures like smile. Both her brain CT and later on MRI showed normal findings as did chromosomal analysis and metabolic screening. Since childhood she had suffered from startle, hand tremor, lengthy whole body shivering on daily basis. These symptoms were provoked by defecation and also lifting legs while lying and on the contrary

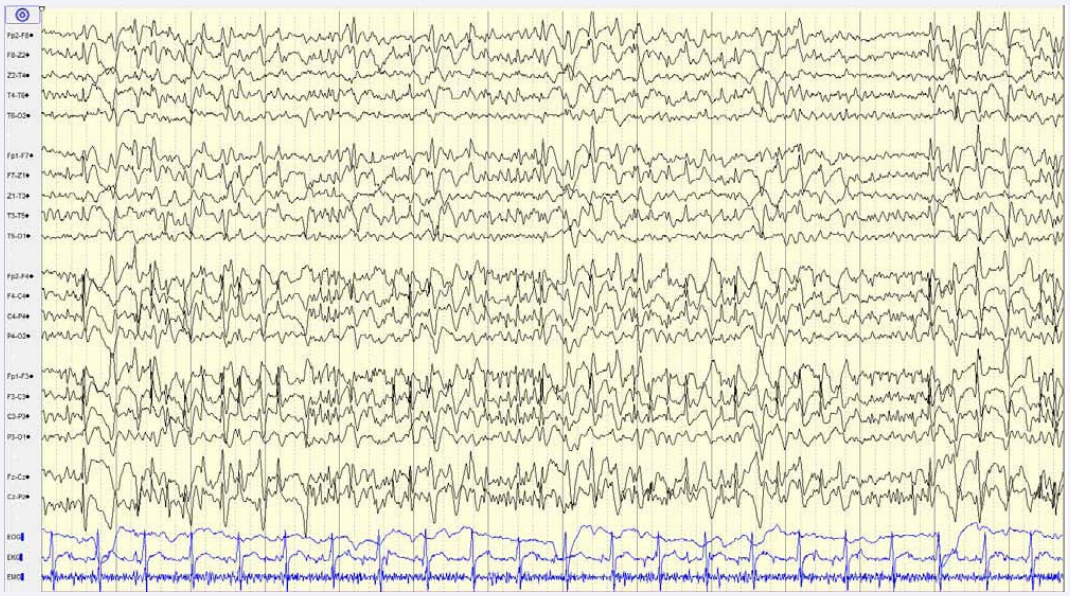

Figure 1 Throughout the EEG-registration occurred runs of 2,7- 3,1 Hz generalized spike-slow wave discharges usually with a duration of several seconds, partly the generalized spike-wave activity is interrupted by short-lasting (usually about one second) high-frequent multiple spike activity.
The patient suffered at times from flailing or shaking movements of the upper limbs especially in connection with the more continuous appearance of the above mentioned spike-slow-wave activity and appeared drowsy and further showed at times twitching movements of the oral region.

restrained by grasping nose. A peculiar sign was stiffening of upper arms while undressing shirt, which was often followed by a fierce falling and shivering for hours. After rectal diazepam, the patient had a long night sleep but the symptoms did often continue after awakening. The seizure description seemed atypical for epilepsy and the seizures did not respond to traditional AEDs (valproate, levetiracetam, lamotrigine, topiramate, clobazam, oxcarbazepine, phenobarbitone, zonisamide, carbamazepine, clonazepam). Therefore, in spite of ictal video-EEG abnormalities (Figure 1) her seizure episodes were classified under movement disorders. AEDs were gradually withdrawn, without any change in condition. Also, psychotropic drugs (haloperidole, risperidone, ketiapine) had been tried without any clinical response. Finally, additional etiological studies were considered and she was referred to a molecylecaryotype testing, which showed maternal deletion in chromosome 15 confirming AS. The epileptic nature of the symptoms were reconsidered after a literature search of AS and epilepsy (4-3) gave a hint of MSNPS, and an orphan drug (indicated for another severe myoclonic epilepsy namely Dravet syndrome) was initiated. Stiripentol 2000mg/day combined to clobazam 10mg/day has so far shown a good response (75% seizure frequency) allowing her to walk using a walker and participate in daily activities instead of being bed-ridden.

DISCUSSION

Appropriate management of intellectually disabled patients with rare diseases is commonly delayed due to diagnostic challenges as well as a poor general knowledge of the natural course of these rarities and their related comorbidities. In our case long-lasting neuropsychiatric symptoms were mistaken for years as movement disorders until a new molecule-genetic testing and reanalysis of video-EEG recording (together with literature search) revealed the right diagnoses, i.e. AS and MSPS behind ID and neuropsychiatric symptoms, respectively. Also, the general thought of AS being “a happy puppet syndrome” may have misled us at the beginning because a more characteristic term for our patient’s syndrome would have been “an unhappy puppet” syndrome. Perhaps the unusual appearance in our AS case was caused by MSPS as some of the patients with that particular epilepsy have been described to appear apathetic.

There are no specific treatment recommendations for patients with AS suffering from MSNPS, which necessitates individually tailored experimental trials, i.e. the literature search and the best available clinical knowledge. Stiripentol was chosen for our patient, because it is an orphan drug indicated for severe myoclonic epilepsy of infancy, i.e Dravet syndrome. Patient’s response to stiripentol turned out to be surprisingly good after several failures seen with conventional AEDs and antipsychotic medicines.

This case is a representative example of how treatment resistant neuropsychiatric symptoms in intellectually disabled patients can be overcome by right diagnostics that requires multidisciplinary expertise and literature search. The clinical outcome of our patient was remarkable; before AS and MSPNS were diagnosed she was bed-ridden, but since the initiation stiripentol combined to clobazam she has literally been able to leave her bed and walk.

REFERENCES

1. Buiting K, Williams C, Horsthemke B. Angelman syndrome - insights into a rare neurogenetic disorder. Nat Rev Neurol. 2016; 12: 584-593.
2. Helbig I, Tayoun AA. Understanding Genotypes and Phenotypes in Epileptic Encephalopathies. Mol Syndromol. 2016; 7: 172-181.
3. Elia M. Myoclonic status in nonprogressive encephalopathies: an update. Epilepsia. 2009; 5: 41-44.

4. Bjelogrlic-Laakso N, Aaltonen S, Dorn T, Arvio M. Need for special units for the management of neuropsychiatric disorders in people with intellectual disabilities. Acta Psychiatr Scand. 2014; 130: 77-79.

5. Döring JH, Lambert A, Hoffmann GF, Ries M. Thirty Years of Orphan Drug Legislation and the Development of Drugs to treat Rare Seizure Conditions: A Cross Sectional Analysis. PLoS One. 2016; 11: e0161660.

Cite this article

Arvio M, Nyrke T, Müller M, Bjelogrlic-Laakso N (2017) Epileptiform Discharges in a Patient with Angelman Syndrome. J Autism Epilepsy 2(1): 1013.