TITLE

Atypical benign partial epilepsy and a new variant of SLC35A3 gene plus 2p25.1 duplication.

Phenotypic-Genotypic correlation?

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SHORT TITLE: ABPE and new Phenotypic-Genotypic correlation

Keywords: Atonic seizures, pseudo-Lennox syndrome, Continuous Spike-Wave during Sleep (CSWS), Electrical Status Epilepticus during Sleep (ESES), phenotypic-genotypic correlation.
Abstract

Background
Atypical Benign Partial Epilepsy (ABPE), recognized also as pseudo-Lennox syndrome, is an uncommon form of epilepsy characterized by generalized minor seizures such as atonic, absences, or myoclonic seizures, and electroencephalographic pattern of focal or multifocal sharp waves with activation of epileptiform discharges during sleep. ABPE is indicated as a variant of ESES (ILAE classification 2017). ESES is a clinical entity that is characterized by encephalopathy with cognitive/behavioral regression and EEG pattern of electrical status epilepticus during slow sleep. Fine and gross motor, language and social/behavioral impairment are associated symptoms, which may have reversible or persistent course. ABPE has been ascribed to the group of the “epilepsy aphasia spectrum” disorders, which includes also Rolandic Epilepsy, Landau-Kleffner syndrome, and electrical status epilepticus during sleep/continuous spike-wave during sleep. We report a young boy with a previous mild motor and language delay, who at 2-year-old presented with recurrent atonic seizures and an EEG pattern consisting of continuous spike and waves during sleep.

Methods
Next Generation Sequencing and microarray technology were used to investigate the molecular background of the proband, and the findings were then analyzed and integrated with clinical data.

Results
The child has been followed up to 7 years of age showing a progressive, complete EEG resolution and a normalization of the previous motor and cognitive impairment in association to the levetiracetam treatment. Genetic diagnosis displayed a novel heterozygous mutation c.310G>A of the SLC35A3 gene and a partial duplication of the short arm of chromosome 2, which might have pathogenic correlation with the neurological signs presented by the child.

Conclusions
Data generated by a genomic approach disclose a more comprehensive view of the genotype-phenotype correlation analysis for the novel pathogenic variant and ABPE. The relationship between the phenotypic manifestations of the child and genetic data is discussed.

**Background**

Clinical aspect of atypical benign partial epilepsy (ABPE) was first described by Aicardi and Chevrie [1] in seven children who showed benign clinical course not compatible at the differential diagnosis with those recognized to be more severe and more complex as reported in patients with myoclonic-astatic epilepsy (MAE) [2]. In the report of Aicardi and Chevrie [1], the children showed several types of seizures mainly partial motor, atypical absence, and myo-atic seizures with onset of symptoms between the ages of 2 years and 5 months to six years. In these children, aside from the epileptic seizures, neither cerebral anomalies nor neurologic dysfunctions including developmental delay/intellectual disability (DD/ID) were reported. To note, the EEG showed a striking contrast between the registration carried in the awake presenting with focal paroxysms and the record during the sleep, which showed an almost continuous, diffuse, slow spike-wave activity. The seizures disappeared spontaneously in all the seven children. Aicardi and Chevrie [1] evaluating the clinical benign characteristic of the disorder introduced the term ABPE. More recently, ABPE has been recognized as a variant of ESES and is included in the ILAE classification [3]. ESES is a clinical entity presenting with encephalopathy and cognitive/behavioral regression and with typical electroencephalographic patterns of continuous or almost continuous spike and wave activity during NREM sleep [4]. In this disorder, the prognosis is variable with loss of already acquired abilities in fine and gross motor, language, and social/ behavioral domains, or with a benign evolution with complete recovery [5-8].

Aside from ABPE, which manifests with a more benign course [9-14], features of typical EEG anomalies associated with neurologic disturbances are seen in ESES and continuous spike and wave during sleep (CSWS), which are defined as a unique shared entity, called with the unified acronym
“ESES/CSWS”, and in Landau-Kleffner syndrome (LKS), also called as acquired aphasia syndrome.

The inclusion of LKS in the ESES group has been recently suggested [15].

We report a 7-year-old boy who showed a previous mild DD in motor and language domain. He displayed at the age of 2 years recurrent atonic seizures with ESES recording. An atonic seizure was registered during the Video-EEG recording. We have followed serially up the child with clinical examination and EEG record reporting a constant, progressive improvement as regard both motor and language domains. Treatment with levetiracetam coincided with a regression of the clinical and EEG signs. At the present age of 7 years, the boy shows a normal motor function, language skill and EEG record. Genetic investigation based on Array Comparative Genome Hybridization (aCGH) revealed a partial duplication of short arm of chromosome 2 that includes five genes (ASAP2, ITGB1BP1, CPSF3, IAH1 and ADAM17), and from the custom-targeted Next Generation Sequencing (NGS) panel for EE a new missense mutation in SLC35A3 gene was displayed (c.310G>A; p.Ala104Thr). A likely pathogenetic phenotype-genotype correlation is proposed.

**Case Report**

A 2-year-old boy was first referred to the University-Hospital “Policlinico-Vittorio Emanuele”, in Catania (Italy) for consultation due to recurrent seizures. He is the first born of healthy unrelated parents. The family history is negative for neurologic disorders. At the conception, the mother was 32 and the father 34 years old. The mother denied having infectious diseases during her pregnancy or to have used drugs or alcohol. Fetal ultrasound examination was normal, as well as fetal movements. The boy was born at 42 weeks of gestation after a normal pregnancy and normal delivery. At the birth, his weight was 3.6 Kg, height 50 cm, and head circumference 35 cm (all within normal range). The development steps were slightly delayed in motor (delay in walking) and in language (first word at the age of 16 months). Sphincter control was reached at a normal age. At the age of 24 months, the child presented critical events consisting of sudden and rapid loss of muscle tone, ahead or behind, or laterally mainly in the right side, of short duration (a few seconds) apparently without loss of consciousness with a high frequency (20-30 episodes per day), preceded by pre-ictal warning signs.
At the admission, the boy weighted 14 Kg, height was 90 cm and head circumference 49 cm (all within normal range). No malformation anomalies were present. Abundant hair was noted in the lateral sides of the forehead and with a linear course along the spinal tract. Ear, heart, and respiratory and abdominal organs were normal. Upon neurological examination, the cranial nerves, patellar reflexes, sensitivity, coordination, and neurovegetative functions were normal. He walked by support and muscular tonus was slightly reduced. The behavior was immature type with poor language for age, but a good social relationship, showing a harmonic performance profile for 24 months of age according to the Griffith Mental Developmental Scales (GMDS). Routine laboratory analyses were normal, including urinary organic acids, urine amino acids, isoelectric focusing of serum transferrin, and echocardiogram. The video-EEG record showed in awake slow bilateral polyspike and wave discharges at the high voltage more evident in the frontal regions. During sleep, the EEG displayed a pattern of continuous and diffuse paroxysms of spike and wave ESES type for more than 85% of the record (Figure 1). Audiometric tests and ophthalmologic examination were normal. A brain MRI showed a widened cisterna magna (35x25 mm). At the age of 31 months, the child presented according to GMDS scale, a performance in locomotor, personal-social, hearing and language, eye and hand coordination related to children of 24-months.

Initial treatment with sodium valproate (20 mg/kg/day) was subsequently increased to 30 mg/kg/day with partial control of the seizures, but a subsequent EEG 6 months later was unchanged. A negative myoclonus seizure with loss of head control was registered on the video-EEG, which showed spike discharges and slow waves prevalent in the fronto-centro-temporal areas (Figure 2). At the age of 3 years, ethosuximide (20 mg/kg/day) as an add-on was introduced. This treatment reduced the frequency of seizures, but these continued to be present at a frequency of five episodes per day. In this phase, the EEG anomalies were less evident. At the age of 4 years, valproate was reduced to complete withdrawal, and levetiracetam was added to ethosuximide with rapid and consistent regression to disappearance of the epileptic seizures. At the age of 4 years and 6 months, no seizures were reported. At this age, physical examination showed a weight of 15 kg, height of 105 cm, and
head circumference of 49.5 cm (all within the normal range). At primary school, he interacted well with the other children, with sufficient scholastic performance and IQ measured 70 at the WISC scale. Hair was present in the limbs and trunk but were less abundant than before. An EEG recorded during sleep showed the presence of spikes in the fronto-central areas (Figure 3). At the most recent examination at the age of 7 years, EEG was normal. Teachers had reported that the child has reached a discrete scholastic performance and a good semantic range of language ability. Genetic analysis of EE revealed a heterozygous state for mutation c.310G>A of the gene SLC35A3 and a partial duplication of the short arm of chromosome 2.

Method
Genetic Testing
Genomic DNA was isolated from peripheral blood of the proband. aCGH analysis was carried out by CytoChip ISCA 8x60K v.2.0 (Cambridge Bluegenome, Illumina Inc., San Diego CA, USA) according to the manufacturer's recommendations. aCGH data were analyzed and interpreted using BlueFuse multi software v.4.2 (GRCh38 assembly).

Using a custom HaloPlex target enrichment system (Agilent Technologies, Santa Clara, CA), a gene panel testing in EE was performed on the Illumina MiSeq platform (Illumina, Inc. San Diego, CA). The EE panel included 23 genes: ALDH7A1 (NM_0011182.2), PNPO (NM_018129.3), ARHGEF9 (NM_015185.2), SLC25A22 (NM_1191060.1), PLCB1 (NM_015192.3), TBC1D24 (NM_001199107.1), PNKP (NM_007254.3), KCNT1 (NM_020822.2), KCNQ2 (NM_172107.2), SCN2A (NM_02/1007.2), SCN8A (NM_014191.3), STXBP1 (NM_003165.3), SCNIA (NM_001165963.1), PCDH19 (NM_001184880.1), CDKL5 (NM_003159.2), SPTAN1 (NM_001130438.2), SLC2A1 (NM_006516.1), ST3GAL3 (NM_174963.3), GRIN2A (NM_001134407.2), CHD2 (NM_001271.3), HCN1 (NM_021072.3), SYNGAP1 (NM_006772.2), SLC35A3 (NM_012243.2).
For NGS data analysis was used CLC Genomics Workbench v. 20.0 and SureCall software 3.0. For the clinical and functional interpretation of genomic variants was used Alamut-Batch v.1.4.0, and PolyPhen-2 v.2.2.2. Variants were annotated for minor allele frequencies in the Genome Aggregation Database (gnomAD) database v.3, and heterozygous variants with minor allele frequencies >0.01 (1%) were filtered out. Clinical interpretation and classification of variants as pathogenic/likely pathogenic/Variant of Uncertain Significance (VUS)/likely benign/benign was done according to the 2015 American College of Medical Genetics and Genomics (ACMG) guidelines [16]. To validate variants from NGS findings, and to investigate regions covered less than 20X was done the Sanger sequencing on ABI 3130/3730 (ThermoFisher Scientific). The analysis of sequenced fragments was performed using SeqCap software v. 2.7. Predictive tools for in silico mutational analysis, such as Provean (http://provean.jcvi.org/index.php), and MutationTaster (http://www.mutationtaster.org/) were used.

**Results**

The aCGH analysis revealed a partial duplication (425 kb) of chromosome 2p25.1 with the following rearrangement: arr(hg19) 2p25.1 (9,248,764-9,674,107)x3. The detected region in which five genes (ASAP2, ITGB1BP1, CPSF3, IAH1, and ADAM17) are located, has not been known as a disease associated CNV in the Database of Genomic Variants (http://dgv.tcag.ca/dgv/app/home).

Additionally, a novel heterozygous missense variant (c.310G>A) of the SLC35A3 gene (NM_012243.2) was identified by EE gene panel testing. According to the Human Gene Mutation Database and further in-silico analysis, the detected variant (dbSNP138), which has not been previously described in the literature, leads to non-synonymous substitution of alanine 104 to threonine (p.Ala104Thr) and is present in a highly conserved site of the transmembrane domain, thereby introducing a deleterious change in the physicochemical properties of the protein encoded by the SLC35A3 gene.
We report on a child affected previously by mild motor and language delay, who at the age of 2 years presented with recurrent atonic seizures and a typical EEG pattern of spikes and waves occurring in more than 85% of the sleep recording.

The first seizures were observed at the age of 2 years with recurrent episodes of loss of muscle tone and head control, forward and downward, in rapid sequences of short duration. At admission, the neurological examination confirmed the motor and language delay, and a widened cisterna magna was reported in the brain MRI. Hematological laboratory analyses were normal. One of the negative myoclonic seizures was registered at the awake EEG recording. The clinical course of the child was good with gradual motor and language improvement and led to reduction and disappearance of seizures and EEG epileptiform discharges when levetiracetam was added to ethosuximide. At present, the 7-year-old child is seizure-free, and he attends the primary school normally.

Atonic seizures present with sudden loss of muscle tone, that last a few seconds, and which can affect the head, body, arms, and legs [13, 17]. The seizures usually have a high frequency with mild to no post-ictal events. Among the several types of seizures in children, atonic seizures are reported to be less common [17]. Atonic seizures are often a part of epileptic syndromes, and rarely occur as isolated manifestations; however, more frequently, they appear together with the other types of seizures, as observed in the well-known syndromes, such as myoclonic astatic epilepsy (MAE), epilepsy with myoclonic-atonic seizures (EMAS) [10, 18], and LGS [19]. Defining features, diagnostic criteria, and the relationship among ESES, CSWS, and ABPE, are a matter of debate [19] because all share common electro-clinical features and minor clinical differences. Aside ABPE other terms are used such as atypical Rolandic epilepsy, and more recently atypical childhood epilepsy with centrotemporal spikes and all designed on the term epilepsy-aphasia. The incidence of each of these disorders is unknown. In a recent study carried out in fourteen patients with ESES, Raha et al. [20] reported nine patients with CSWS/ESES syndrome, three with atypical benign partial epilepsy of childhood with centrotemporal spikes (BECTS), one with opercular syndrome, and one with LKS.
The duration of typical EEG anomalies ranged from 6 to 52 months in 91% of the cases, and in 53% of the cases, borderline or moderate cognitive impairment was noted. In a report by van Hirtum-Das et al. [21], among 90 patients with ESES, 18 had a diagnosis of LKS.

ESES has been defined as an age-related epileptic encephalopathy with characteristic EEG patterns in patients presenting with various seizure types, different etiologies, variable prognoses, and signs of cognitive and behavioral deterioration related to a significant and sustained activation of EEG during NREM sleep [5-7, 15, 22]. The most representative features of the disorder include several types of seizures, namely as focal motor seizures, complex focal seizures, and other seizure types, including clonic, tonic-clonic, absences, atomic, and myoclonic seizures. The neuropsychological and/or motor impairment found in ESES patients has been hypothesized to be linked to the prolonged, sleep-related focal epileptic activity, which affects the sleep pathway and causes severe damage through disruption of the cortical plasticity processes [22].

ABPE is an uncommon form of focal idiopathic epilepsy presenting with multiple seizure types, an EEG record with focal and/or generalized epileptiform discharges, with sustained epileptic activity during NREM sleep, and a variable neurocognitive deficit [23]. In a study of 43 children with ABPE, cognitive impairment preceding the onset of epileptic seizures was reported in 26% of the patients [24]. The authors reported that the onset of epilepsy occurred between 2 and 6 years of age in 74% of the patients, and 67% presented with generalized minor seizures. Among these, 28% showed simple partial seizures of the oro-facial region or generalized tonic-clonic seizures starting from the oro-facial region. Additionally, 44% of the patients showed generalized tonic-clonic, 21% unilateral, 44% partial motor, 12% versive, 9% focal atomic, and 24% complex-partial seizures. An electroclinical status epilepticus was found in 56% of the patients during sleep. In this group of patients, no tonic seizure types were observed. After following up till the age of 15 years, 84% of them were in clinical remission and no seizures were registered. Cognitive impairment was reported in 56% of the cases. This study also confirmed that ABPE broadly overlapped with Rolandic epilepsy (RE), ESES, and LKS [24]. Severe global and specific cognitive disturbances have been reported.
almost constantly in 30 ABPE/ pseudo-Lennox syndrome (PLS) patients enrolled by Japaridze et al. [25]. According to these authors, at the time of epileptic seizures, the presentation of cognitive level was lower than the standard range and remained unchanged during the disease process. The authors concluded that EEG, duration of epilepsy, and treatment did not influence cognitive impairment, as global and specific cognitive disturbances were almost constantly present and did not show any improvement during the disorder or after the antiepileptic treatment [25]. Allen et al. [23] reported a boy with ABPE who after a very active seizure period manifested acquired oral-motor, language, social communicative, and neurocognitive manifestations, followed by lexical semantic impairment. During the follow-up from the age of 5 to 13 years, the child manifested an improvement in EEG seizure control with residual specific disorder of lexical semantics involving both receptive and expressive vocabulary.

The main clinical characteristics presented in our case are consistent with a diagnosis of ABPE in consideration of focal idiopathic epilepsy with typical EEG pattern, recurrent episodes of atonic seizures, and benign course with a progressive normalization of the clinical and EEG features in association with antiepileptic treatment. It should be noted that motor and language delay preceded the onset of epileptic seizures and did not worsen during the epileptic course, and therefore should not be temporally related to the onset of epileptic events.

The molecular analysis identified in this patient is noteworthy. The child carries a novel heterozygous pathogenic \textit{SLC35A} variant (p.Ala104Thr) and partial duplication of 2p. The \textit{SLC35A3} gene (NM_012243.2) encodes the major Golgi uridine diphosphate-n-acetylglucosamine (UDP-GLCNAc) transporter, which has been recently added to the list of genes for epilepsies [26-29]. However, further investigations are needed to characterize the role of the gene in the pathogenesis of electroclinical syndromes. Second, the duplication of 2p that comprises five genes (\textit{ASAP2}, \textit{ITGB1BP1}, \textit{CPSF3}, \textit{IAHI}, and \textit{ADAM17}) has not been reported in large-scale genetic studies for the etiology of epileptic encephalopathy (EE) [29-31]. Therefore, the chromosomal abnormality observed in this child appears to be the first report of ABPE-affected patients, and we
cannot delineate a pathogenic role for the rare CNV detected. With extension of the analysis to a set of functional annotations of genes in the same CNV, we attempted to depict a potential modulation of EE pathogenesis. The resulting evaluation showed that, in a study of gene profiling of hippocampal tissues of rat samples, the Asap2 (ArfGAP with SH3 domain, ankyrin repeat, and PH domain 2) gene was involved in the focal cortical dysplasia (FCD) and intractable epilepsy [32].

Integrin subunit beta 1 binding protein (ITGB1BP1) is recognized as a potential epilepsy-associated gene [33]. Cleavage and polyadenylation specific factor 3 (CPSF3) and isoamyl acetate-hydrolyzing esterase 1 homolog (IAH1) genes are not strongly correlated with the risk of developing seizure disorders, but both play a synaptic activity putatively involved in several neurological and psychiatric disorders [34-35]. Dysfunction of ADAM17 (ADAM Metallopeptidase Domain 17), as in the other ADAM family member proteins, is known to be involved in a wide variety of neuropathologies and epileptic seizures [36-37]. Thus, the increasing interest in supporting the genetic risk of CNV for epilepsies allows better examination of the CNV carriers of unexplained cases, thus helping clinical reporting [38]. The treatment of ESES, ABPE, and LKS may include old and new anti-epileptic drugs, alone or in combination with valproic acid, ethosuximide, sulthiame, and steroids, and immunoglobulins [39]. Ketogenic diet and surgery with multiple subpial transactions led to good results in terms of both reduction in epileptic seizures and cognitive development [40-41]. In general, treatment of ESES and related disorders is suggested to be carried out with a combination of valproic acid with other anticonvulsant drugs.

In a reanalysis conducted by Kelley and Kossof [41] on six papers reporting the treatment of ESES with ketogenic diet, an overall EEG improvement was observed in 53% of the patients; 41% of the patients had a seizure reduction beyond 50%, and 9% showed a normalization of EEG. Cognitive improvement was observed in 45% of the patients. van den Munckhof et al. [40] collected 112 articles regarding the treatment of electrical status epilepticus in 575 patients. Antiepileptic drugs (AEDs) showed improvement in both cognitive and EEG patterns in 49% of the patients and in 68% specifically with benzodiazepines [40]. Improvement was also registered in 81% of the patients with
steroids and in 90% of the patients with surgery. The authors observed that better prognostic results were obtained both in patients with normal development before the disorder and in the absence of cerebral structural abnormalities [40]. However, the use of benzodiazepine (BZD) is not always recommended for the high risk of GABAa receptor desensitization. Corticosteroids should be reserved to avoid cognitive stagnation or regression. Similar to the experience of Zhang et al. [42] for the result reached in a single patient, in our case, we achieved a rapid improvement in EEG record with disappearance of seizures shortly after administration of levetiracetam as an add-on to ethosuximide. No further abnormalities in a follow-up period of 2 years were registered.

Conclusions

The field of research in the ESES with clinical neurologic involvement is fascinating. In this boy, the severe initial manifestations had a progressive improvement and treatment with levetiracetam may have contributed to get better the course of the disorder. The potential role of gene mutation and structural abnormality observed in the child remains to be established.

Abbreviations

| Abbreviation | Description                                      |
|--------------|--------------------------------------------------|
| ABPE         | atypical benign partial epilepsy                 |
| aCGH         | array comparative genome hybridization           |
| CNVs         | copy number variants                             |
| CSWS         | continuous spike and wave during sleep           |
| DD/ID        | developmental delay/intellectual disability      |
| EE           | epileptic encephalopathies                       |
| ESES         | electrical status epilepticus during sleep       |
| GMDS         | Griffith mental developmental scales             |
| LGS          | Lennox-Gastaut syndrome                          |
| LKS          | Landau-Kleffner Syndrome                         |
| MAE          | myoclonic-astatic epilepsy                        |
| NGS          | next generation sequencing                        |
Ethical Publication Statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Ethics approval and consent to participate

The study was ethically conducted in accordance with the World Medical Association’s Declaration of Helsinki, and the experimental protocol was approved by the ethics committee of the University of Catania, Italy (Ethical Committee Catania 1 Clinical Registration n. 95/2018/PO). Written informed consent was obtained from the parents.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (and its additional files).

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

EP and PP worked with and helped gather patient data, drafted, and redrafted the present manuscript.

PP, ADP, and RF analyzed and interpreted the patient data regarding the epileptic disease. RC was called as consultants regarding the diagnosis of ESES. XGP was a major contributor in genetic data interpretation. All authors read and approved the final manuscript.
References

[1] Aicardi, J. & Chevrie, J. J. Atypical Benign Partial Epilepsy Of Childhood. Dev Med Child Neurol, 1982:24, 281-92.

[2] Aicardi, J. 1996. Myoclonic-Astatic Epilepsy, London, Chapman & Hall.

[3] Scheffer, I.E., Berkovic, S., Capovilla, S., Connolly, M.B., French, J., Guilhoto, L., et al. Epilepsia. 2017 Apr;58(4):512-521.

[4] Tassinari CA, Dravet C, Roger J. ESES: encephalopathy related to electrical status epilepticus during slow sleep. In: Proceedings of the ninth congress international federation of EEG and clinical neurophysiology. Amsterdam: Elsevier Science, 1977: 529–30.

[5] Mariotti P, D. M. G., Iuvone L, Mennuni Gf, Guazzelli M, Marchetti S, Mazza S. Is Eses/Csws A Strictly Age-Related Disorder? Clin Neurophysiol. 2000: 111, 452-6.

[6] Tassinari, C. A., Rubboli, G., Volpi, L., Meletti, S., D'orsi, G., Franca, M., Sabetta, A. R., Riguzzi, P., Gardella, E., Zaniboni, A. & Michelucci, R. Encephalopathy With Electrical Status Epilepticus During Slow Sleep Or Eses Syndrome Including The Acquired Aphasia. Clin Neurophysiol, 2000: 111 Suppl 2, S94-S102.

[7] Tassinari, C. A., Cantalupo, G., Rios-Pohl, L., Giustina, E. D. & Rubboli, G. Encephalopathy With Status Epilepticus During Slow Sleep: "The Penelope Syndrome". Epilepsia 2009: 50 Suppl 7, 4-8.

[8] Berg A.T. Berkovic S.F. Brodie M.J. et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009 Epilepsia 51 2010 676–685.

[9] Galanopoulou, A. S., Bojko, A., Lado, F. & Moshe, S. L. The Spectrum Of Neuropsychiatric Abnormalities Associated With Electrical Status Epilepticus In Sleep. Brain Dev, 2000: 22, 279-95.

[10] Doose, H., Hahn, A., Neubauer, B. A., Pistohl, J. & Stephani, U. Atypical "Benign" Partial Epilepsy Of Childhood Or Pseudo-Lennox Syndrome. Part Ii: Family Study. Neuropediatrics, 2001:32, 9-13.
[11] Kramer, U., Sagi, L., Goldberg-Stern, H., Zelnik, N., Nissenkorn, A. & Ben-Zeev, B. Clinical Spectrum And Medical Treatment Of Children With Electrical Status Epilepticus In Sleep (Eses). Epilepsia, 2009:50, 1517-24.

[12] Veggiotti, P., Pera, M. C., Teutonico, F., Brazzo, D., Balottin, U. & Tassinari, C. A. Therapy of Encephalopathy With Status Epilepticus During Sleep (Eses/Csws Syndrome): An Update. Epileptic Disord, 2012:14, 1-11.

[13] Caraballo, R. H. & Dalla Bernardina, B. Idiopathic Generalized Epilepsies. Handb Clin Neurol, 2013:111, 579-89.

[14] Issa, N. P. Neurobiology Of Continuous Spike-Wave In Slow-Wave Sleep And Landau-Kleffner Syndromes. Pediatr Neurol, 2014:51, 287-96.

[15] Hirsch, E., Caraballo, R., Bernardina, B. D., Loddenkemper, T. & Zuberi, S. M. Encephalopathy related to status epilepticus during slow sleep: from concepts to terminology. Epileptic Disord, 2019: 21, 5-12.

[16] Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L. & Committee, A. L. Q. A. 2015. Standards and Guidelines for the interpretation of sequence variants: a joint consensus recommendation of the american college of medical genetics and genomics and the association for molecular pathology. Genet Med, 17, 405-24.

[17] Baraldi, S., Farrell, F., Benson, J., Diehl, B., Wehner, T. & Kovac, S. drop attacks, falls and atonic seizures in the video-eeg monitoring unit. seizure, 2015: 32, 4-8.

[18] Kilaru, S. & Bergqvist, A. G. C. current treatment of myoclonic astatic epilepsy: clinical experience at the children's hospital of philadelphia. Epilepsia, 2007:48, 1703-1707.

[19] Kaminska A, I. A., Plouin P, Bru Mf, Dellatolas G, Dulac O. delineation of cryptogenic lennox-gastaut syndrome and myoclonic astatic epilepsy using multiple correspondence analysis. Epilepsy Res., 1999: 36, 15-29.
[20] Raha, S., Shah, U. & Udani, V. Neurocognitive and neurobehavioral disabilities in epilepsy with electrical status epilepticus in slow sleep (eses) and related syndromes. Epilepsy Behav, 2012: 25, 381-5.

[21] Van Hirtum-Das, M., Licht, E. A., Koh, S., Wu, J. Y., Shields, W. D. & Sankar, R. Children With Eses: Variability In The Syndrome. Epilepsy Res, 2006: 70 Suppl 1, S248-58.

[22] Rubboli, G. & Tassinari, C. A. 2019. Encephalopathy Related To Status Epilepticus During Slow Sleep: An Historical Introduction. Epileptic Disord, 21, 3-4.

[23] Allen, N. M., Conroy, J., Deonna, T., Mccreary, D., Mcgettigan, P., Madigan, C., Carter, I., Ennis, S., Lynch, S. A., Shahwan, A. & King, M. D. Atypical Benign Partial Epilepsy Of Childhood With Acquired Neurocognitive, Lexical Semantic, And Autistic Spectrum Disorder. Epilepsy Behav Case Rep, 2016: 6, 42-8.

[24] Hahn, A., Pistohl, J., Neubauer, B. A. & Stephani, U. Atypical "Benign" Partial Epilepsy Or Pseudo-Lennox Syndrome. Part I: Symptomatology And Long-Term Prognosis. Neuropediatrics, 2001: 32, 1-8.

[25] Japaridze, N., Menzel, E., Von Ondarza, G., Steinmann, E. & Stephani, U. Risk Factors Of Cognitive Outcome In Patients With Atypical Benign Partial Epilepsy/Pseudo-Lennox Syndrome (Abpe/Pls) And Continues Spike And Wave During Sleep (Csws). Eur J Paediatr Neurol, 2014:18, 368-75.

[26] Edmondson, A. C., Bedoukian, E. C., Deardorff, M. A., Mcdonald-Mcgin, D. M., Li, X., He, M. & Zackai, E. H. A Human Case Of SLC35A3-Related Skeletal Dysplasia. Am J Med Genet A, 2017: 173, 2758-2762.

[27] Edvardson, S., Ashikov, A., Jalas, C., Sturiale, L., Shaag, A., Fedick, A., Treff, N. R., Garozzo, D., Gerardy-Schahn, R. & Elpeleg, O. Mutations in SLC35A3 cause autism spectrum disorder, epilepsy and arthrogryposis. J Med Genet, 2013: 50, 733-9.

[28] Marini, C., Hardies, K., Pisano, T., May, P., Weckhuysen, S., Cellini, E., Suls, A., Mei, D., Balling, R., Jonghe, P. D., Helbig, I., Garozzo, D., Euro, E. C. A. R. W. G. & Guerrini, R. Recessive
mutations in slc35a3 cause early onset epileptic encephalopathy with skeletal defects. Am J Med Genet A, 2017:173, 1119-1123.

[29] Vlaskamp, D. R. M., Callenbach, P. M. C., Rump, P., Giannini, L. A. A., Dijkhuizen, T., Brouwer, O. F. & Van Ravenswaaij-Arts, C. M. A. Copy Number Variation in a hospital-based cohort of children with epilepsy. Epilepsia Open, 2017: 2, 244-254.

[30] Mefford, H. C., Morrogh, D., Nuernberg, P., Palotie, A., Schoonjans, A. S., Striano, P., Szczepanik, E., Tostevin, A., Vermeesch, J. R., Van Esch, H., Van Paesschen, W., Waters, J. J., Weckhuysen, S., Zara, F., De Jonghe, P., Sisodiya, S. M., Marino, C., Euro, E.-R. E. S. C. & Epi, C. N. V. C. 2019. Diagnostic implications of genetic copy number variation in Epilepsy Plus. Epilepsia, 60, 689-706.

[31] Kessi, M., Peng, J., Yang, L., Xiong, J., Duan, H., Pang, N. & Yin, F. 2018. Genetic etiologies of the electrical status epilepticus during slow wave sleep: systematic review. Bmc Genet, 19, 40.

[32] Wang, J., Lin, Z. J., Liu, L., Xu, H. Q., Shi, Y. W., Yi, Y. H., He, N. & Liao, W. P. 2017. Epilepsy-Associated Genes. Seizure, 44, 11-20.

[33] Kielbinski, M., Setkowicz, Z., Gzielo, K. & Janeczko, K. 2018. Profiles Of Gene Expression In The Hippocampal Formation Of Rats With Experimentally-Induced Brain Dysplasia. Dev Neurobiol, 78, 718-735.

[34] Roussos, P., Guennewig, B., Kaczorowski, D. C., Barry, G. & Brennand, K. J. 2016. Activity-Dependent Changes In Gene Expression In Schizophrenia Human-Induced Pluripotent Stem Cell Neurons. Jama Psychiatry, 73, 1180-1188.

[35] Ravanidis, S., Kattan, F. G. & Doxakis, E. 2018. unraveling the pathways to neuronal homeostasis and disease: mechanistic insights into the role of rna-binding proteins and associated factors. Int J Mol Sci, 19.

[36] Zunke, F. & Rose-John, S. 2017. The Shedding Protease Adam17: Physiology and pathophysiology. Biochim Biophys Acta Mol Cell Res, 1864, 2059-2070.
[37] Hartl, D., May, P., Gu, W., Mayhaus, M., Pichler, S., Spaniol, C., Glaab, E., Bobbili, D. R., Antony, P., Koegelsberger, S., Kurz, A., Grimmer, T., Morgan, K., Vardarajan, B. N., Reitz, C., Hardy, J., Bras, J., Guerreiro, R., Balling, R., Schneider, J. G., Riemenschneider, M. & Aesg 2020. A rare loss-of-function variant of adam17 is associated with late-onset familial alzheimer disease. Mol Psychiatry, 25, 629-639.

[38] Coppola, A., Cellini, E., Stamberger, H., Saarentaus, E., Cetica, V., Lal, D., Djemie, T., Bartnik-Glaska, M., Ceulemans, B., Helen Cross, J., Deconinck, T., Masi, S., Dorn, T., Guerrini, R., Hoffman-Zacharska, D., Kooy, F., Lagae, L., Lench, N., Lemke, J. R., Lucenteforte, E., Madia, F., Doose, H. 1989. Symptomatology In Children With Focal Sharp Waves Of Genetic Origin. Eur J Pediatr, 149, 210-5.

[39] Bahi-Buisson, N., Savini, R., Eisermann, M., Bulteau, C., Dulac, O., Hertz-Pannier, L. & Chiron, C. 2006. Misleading Effects Of Clonazepam In Symptomatic Electrical Status Epilepticus During Sleep Syndrome. Pediatr Neurol, 34, 146-50.

[40] van den Munckhof, B., Van Dee, V., Sagi, L., Caraballo, R. H., Veggiotti, P., Liukkonen, E., Loddenkemper, T., Sanchez Fernandez, I., Buzatu, M., Bulteau, C., Braun, K. P. & Jansen, F. E. 2015. Treatment Of Electrical Status Epilepticus In Sleep: A Pooled Analysis Of 575 Cases. Epilepsia, 56, 1738-46.

[41] Kelley, S. A. & Kossoff, E. H. 2016. How Effective Is The Ketogenic Diet For Electrical Status Epilepticus Of Sleep? Epilepsy Res, 127, 339-343.

[42] Zhang, J., Talley, G., Kornegay, A. L. & Edwards, J. C. 2010. Electrical Status Epilepticus During Sleep: a case report and review of the literature. Am J Electroneurodiagnostic Technol, 50, 211-8.
Figure Legends

Figure 1 – EEG at 28 months. To note, the continuous spike and waves during the slow sleep CSWS type.

Figure 2 – Atonic crisis was registered during EEG record. Spikes and wave prevalent in the fronto-centro-temporal areas during the atonic crisis.

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