

UCLA

UCLA Previously Published Works

Title

Electroencephalographic patterns during sleep in children with chromosome 15q11.2-13.1 duplications (Dup15q)

Permalink

<https://escholarship.org/uc/item/7bj8d88p>

Journal

Epilepsy & Behavior, 57(Pt A)

ISSN

1525-5050

Authors

Arkilo, Dimitrios
Devinsky, Orrin
Mudigoudar, Basanagoud
et al.

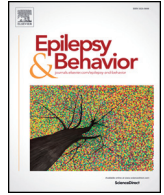
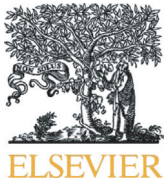
Publication Date

2016-04-01

DOI

10.1016/j.yebeh.2016.02.010

Peer reviewed



Brief Communication

Electroencephalographic patterns during sleep in children with chromosome 15q11.2–13.1 duplications (Dup15q)



Dimitrios Arkilo ^{a,*}, Orrin Devinsky ^b, Basanagoud Mudigoudar ^c, Susana Boronat ^d, Melanie Jennesson ^e, Kenneth Sassower ^f, Okeanis Eleni Vaou ^g, Jason T. Lerner ^h, Shafali Spurling Jeste ⁱ, Kadi Luchsinger ^j, Ronald Thibert ^f

^a Minnesota Epilepsy Group, PA-Children's Hospitals and Clinics of Minnesota, 225 Smith Ave. N, St. 201, St. Paul, MN 55102, USA

^b Department of Neurology, NYU Langone Medical Center, New York University, 240 East 38th Street, 20th floor, New York, NY 10016, USA

^c Comprehensive Epilepsy Program and Neuroscience Center, Le Bonheur Children's Hospital, 848 Adams Ave., Memphis, TN 38103, USA

^d Department of Pediatric Neurology, Vall d'Hebron Hospital, Universitat Autònoma de Barcelona, P. de la Vall d'Hebron, 119-129, 08035 Barcelona, Spain

^e Department of Pediatric Neurology, American Memorial Hospital, CHU Reims, 47 Rue Cognacq-Jay, 51100 Reims, France

^f Department of Neurology, Massachusetts General Hospital, Harvard Medical School, 15 Parkman St., # 835, Boston, MA 02114, USA

^g Noran Neurological Clinic, 2828 Chicago Ave. S., #200, Minneapolis, MN 55407, USA

^h Department of Pediatrics, Mattel Children's Hospital at UCLA, 757 Westwood Plaza, Los Angeles, CA 90095, USA

ⁱ Department of Neurology, UCLA Center for Autism Research and Treatment, 710 Westwood Plaza, Los Angeles, CA 90095, USA

^j Dup15q Alliance, Fayetteville, NY 13066, USA

ARTICLE INFO

Article history:

Received 14 January 2016

Revised 5 February 2016

Accepted 6 February 2016

Available online xxxx

Keywords:

EEG patterns

Sleep

Dup15q syndrome

Children

ABSTRACT

Our objective was to define the EEG features during sleep of children with neurodevelopmental disorders due to copy number gains of 15q11–q13 (Dup15q). We retrospectively reviewed continuous EEG recordings of 42 children with Dup15q (mean age: eight years, 32 with *idic15*), and data collected included background activity, interictal epileptiform discharges, sleep organization, and ictal activity. Three patterns were recognized:

Pattern 1: Alpha–delta sleep was noted in 14 children (33%), not associated with any clinical changes.

Pattern 2: Electrical status epilepticus in sleep was noted in 15 children (35%), all diagnosed with treatment-resistant epilepsy. Thirteen of the 15 children had clinical seizures.

Pattern 3: Frequent bursts of high amplitude bifrontal predominant, paroxysmal fast activity (12–15 Hz) during non-REM sleep was noted in 15 children (35%). All 15 children had treatment-resistant epilepsy.

This is the first report of electroencephalographic patterns during sleep of children with Dup15q reporting alpha–delta rhythms, CSWS, and high amplitude fast frequencies. Alpha–delta rhythms are described in children with dysautonomia and/or mood disorders and CSWS in children with developmental regression. The significance of these findings in cognitive function and epilepsy for the children in our cohort needs to be determined with follow-up studies.

© 2016 Elsevier Inc. All rights reserved.

1. Introduction

Copy number gains of the 15q11.2–13.1 region (Dup15q) in the maternal chromosome give rise to a neurodevelopmental disorder characterized by variable severity of intellectual disability, motor

delay, autism spectrum disorder (ASD), language impairment, psychosis, and/or epilepsy. The most frequent chromosomal rearrangements are an extra, isodicentric chromosome 15 (*idic15*) or inverted duplication 15 and interstitial duplication of 15q11–q13 (*int dup15*) [1,2].

Most reports on the epileptic phenotype and electroencephalographic (EEG) findings relate to *idic15*. Seizures occur in two-thirds of these patients: most begin between six months to nine years of age and are treatment resistant [1,3]. The spectrum of seizure types includes infantile spasms and generalized tonic–clonic, atonic, tonic, or focal seizures. Electroencephalographic abnormalities include hypsarrhythmia; focal, multifocal, or/and generalized spikes; and diffuse fast rhythms

* Corresponding author. Tel.: +1 6512415290; fax: +1 6512415680.

E-mail addresses: arkdim@hotmail.com (D. Arkilo), od4@nyu.edu (O. Devinsky), bmudigoudar@hotmail.com (B. Mudigoudar), susboronat@gmail.com (S. Boronat), meljennesson@yahoo.fr (M. Jennesson), ksassower@mg.harvard.edu (K. Sassower), dimiar@hotmail.com (O.E. Vaou), jlerner@mednet.ucla.edu (J.T. Lerner), sjeste@mednet.ucla.edu (S.S. Jeste), kadi.luchsinger@dup15q.org (K. Luchsinger), rthibert@mg.harvard.edu (R. Thibert).

[4–8]. The clinical and EEG findings are often consistent with Lennox–Gastaut syndrome. There are limited data on the epilepsy phenotypes in other Dup15q rearrangements, with reports of ‘temporal spikes during sleep’ or ‘focal epilepsy’ [8,9].

Although children with Dup15q are frequently evaluated in epilepsy monitoring units, their sleep EEG patterns are not well described. This study sought to define the EEG features during sleep of a clinic-referred cohort of children with neurodevelopmental disorders due to copy number gains of 15q11–q13. This is the largest report detailing the sleep EEG patterns in this cohort.

2. Material and methods

We retrospectively reviewed records of long term continuous EEG recordings (including at least one night of recording) of children with Dup15q syndrome admitted in five level four epilepsy monitoring units (Massachusetts General Hospital, New York University Langone Medical Center, Minnesota Epilepsy Group–Children’s Hospital and Clinics of Minnesota, Le Bonheur Children’s Hospital, Mattel Children’s Hospital–UCLA). All centers have certified specialty clinics for children with Dup15q. For all the patients, the genetic diagnosis of neurodevelopmental disorder due to a copy number gain of 15q11–q13 was confirmed by microarray or FISH analysis. Electroencephalographic studies were obtained to evaluate for possible or definite seizures and were reviewed and scored manually by five board-certified epileptologists and two sleep medicine specialists. Data collected included background activity, interictal epileptiform discharges, sleep organization, and ictal activity. The standard international 10–20 system electrode placement was used including bilateral anterior temporal electrodes. Primarily referential and bipolar montages were used for EEG review, as well as specifically reformatted arrays when necessary. Videos were reviewed when available. This study was approved by the institutional review board at all five sites: Informed consent for the admission and EEG evaluation was obtained verbally and in writing when the patients presented for their hospitalization.

3. Results

Forty-two children were included (22 males) with mean age of eight years (range: 0–16 years). Thirty-two children had *idic15*, and 10 had

int dup15. Twenty-eight patients with *idic15* and one with *int dup15* (29/42, 69%) had epilepsy and were being treated with at least one antiepileptic medication(s) (AED, mean: 2.5 AEDs). All children with epilepsy had moderate to severe intellectual disability, met DSM V criteria for autism spectrum disorder, and had multiple seizure types including generalized tonic–clonic, tonic, atonic, and focal clonic seizures and myoclonic epileptic spasms. We observed the following three EEG patterns in the cohort.

Pattern 1 Alpha–delta sleep occurred in 14 children (33%, nine with *idic15*) for which the data were available. Alpha–delta sleep in nonrapid REM sleep was defined as the appearance of prominent alpha activity (frequency of 8–13 Hz) on delta waves (frequency of 0.5–2 Hz). The duration of alpha–delta sleep ranged from 4 to 20 s. At least seven children were on benzodiazepines during the recordings. There were no clinical changes associated with this pattern (Fig. 1).

Pattern 2 Fifteen children (35%, all with *idic15*) had electrical status epilepticus in sleep (ESES). Electrical status epilepticus in sleep was defined as continuous unilateral or bilateral epileptiform activity that occupied more than 50% of slow wave sleep. Thirteen out of the 15 children have clinical seizures. Ten children had speech and gross motor developmental regressions in the first four years of life. For the patients within this group, there was lack of normal sleep architecture with less distinct transitioning through sleep states and decreased frequency of sleep spindles and central vertex waves of sleep.

Pattern 3 Fifteen (35%, 14 with *idic15*) had frequent bursts of high amplitude (up to 450 μ V), bifrontal predominant, paroxysmal fast activity (12–15 Hz) during non-REM sleep that disrupted the sleep architecture. This intermittent beta activity lasted 5 to 60 s and was maximal in frequency and amplitude during the early sleep; it decreased or dissipated during stage four of sleep versus stages two and three. This pattern was not stimulus-triggered, and at times, there appeared to be some subtle tonic posturing associated with these events, but this was not common. This tonic posturing was not determined by any of the EEG readers to fit the criteria for clinical seizures. All 15 children had treatment-resistant epilepsy, 10 with

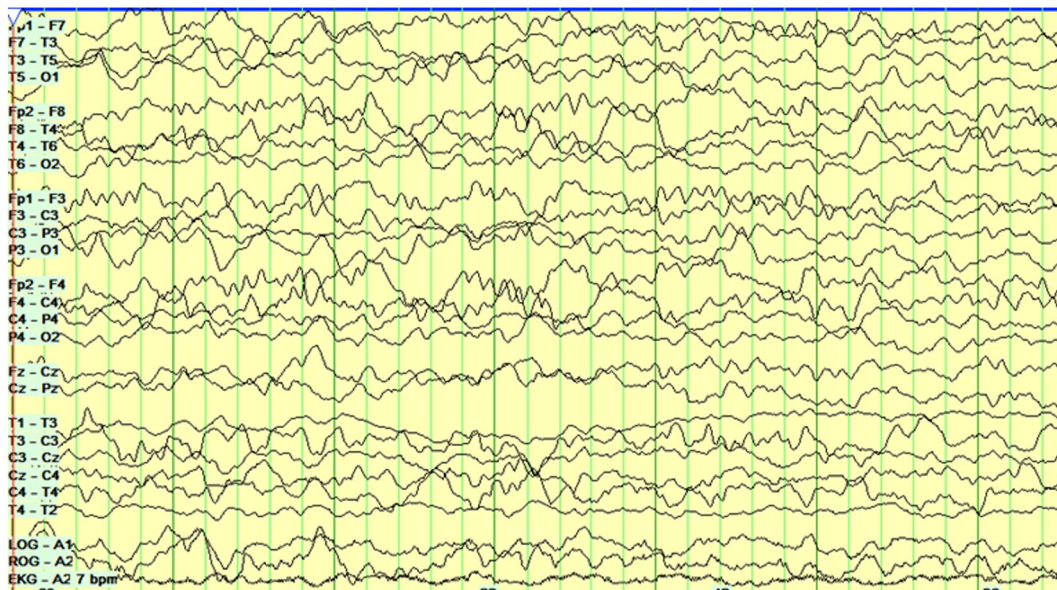


Fig. 1. Example of alpha–delta pattern in non-REM sleep.

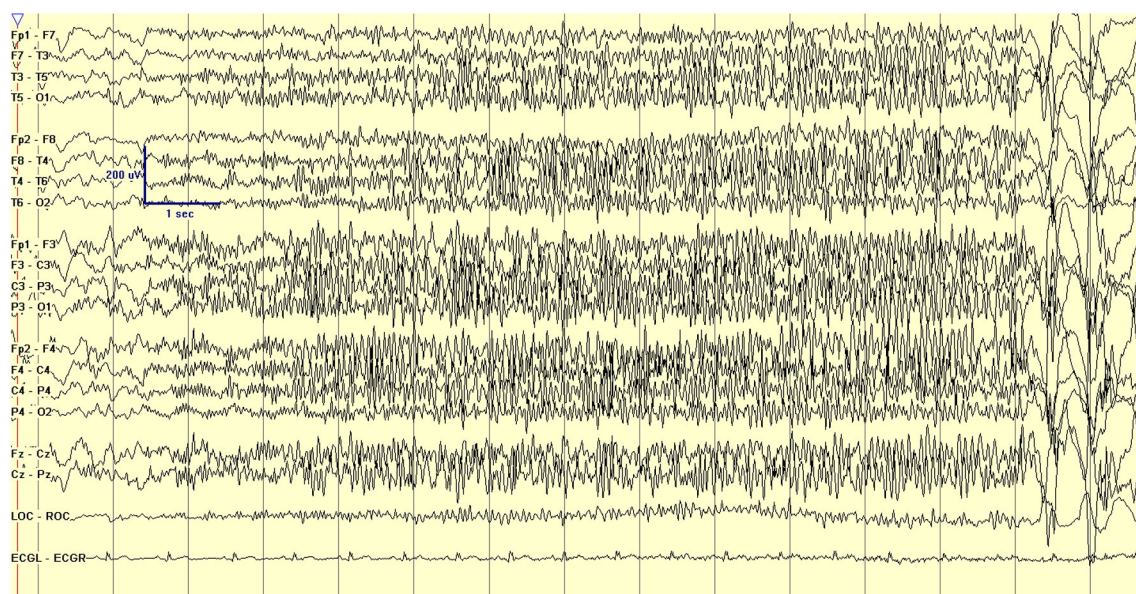


Fig. 2. Example of bursts of high amplitude, bifrontal predominant, sharp fast activity during non-REM sleep.

Lennox–Gastaut syndrome, and seven were being treated with benzodiazepines during the recording (Fig. 2).

4. Discussion

We identified three common sleep patterns in patients with Dup15q. Alpha–delta sleep is characterized by alpha wave intrusions (8–13 Hz) on delta waves during non-REM sleep. This occurs in patients with nonrestorative sleep, chronic fatigue syndrome, fibromyalgia, and depression [10,11]. These disorders are associated with reduced sleep efficiency, but alpha–delta sleep is not known to directly decrease sleep efficiency. The underlying pathophysiology or potential effects of alpha–delta sleep remain poorly defined.

The epileptic encephalopathy, continuous spikes and waves during sleep (CSWS), is a clinical syndrome associated with developmental regression, seizures, and an EEG pattern of ESES. It is an age-related condition in children and adolescents occurring in 0.5% of patients with epilepsy [12]. The most common presentation of CSWS is a sleep-related seizure in a child with normal neurocognitive function prior to CSWS onset [12]. Cognitive regression typically occurs within 2–3 years (age of onset: 4–7.7 years) [12]. The pathophysiology of CSWS is poorly understood. Impaired feed-forward inhibition of thalamocortical neurons may create a pathological reinforcing loop in an oscillatory corticothalamic network [13]. The ILAE criteria do not specify a minimum percentage value of ESES when diagnosing CSWS; a range of 50–85% of spike and wave activity occupying non-REM sleep is commonly used [12].

In our cohort, ESES was seen in 35% of the patients, all diagnosed with *idic15*, and at least 66% of them had developmental regression; 86% had a history of seizures. Alpha–delta sleep was seen in 33% of the patients, including children with *int dup15*; it was not associated with any clinical dysfunction. The significance and the specificity of this pattern remain to be determined. It also occurs in other conditions, including pain and autoimmune or mood disorders. The high amplitude paroxysmal fast activity (pattern 3) that disrupted the sleep architecture has not been reported on any other chromosome duplication, even though it is seen in epilepsy syndromes such as Lennox–Gastaut syndrome [14]. This pattern appears to be prominent within our group as well. Thirty-five percent of our patients, all but one diagnosed

with *idic15*, demonstrated this pattern, and all had epilepsy. Since all children with this pattern had medically resistant epilepsy, this pattern may be a biomarker for intractability in this population.

The abnormal sleep patterns we identified likely result from the excess number of genes coded in the *dup15q11-q13* region. This is a unique portion of the human genome, with many imprinted genes. Since the phenotype is more severe in children who received the duplication from the maternal 15, the role of *UBE3A* and *ATP10A* may be especially relevant. Reduced *UBE3A* function likely contributes to the pathogenesis of Angelman Syndrome while overexpression likely contributes to Dup15q. This gene codes for a protein that degrades E3 ubiquitin ligase and regulates intracellular protein levels; it also is a transcriptional regulator of nuclear steroid hormone receptors. Further, three GABA receptor genes (*GABRB3*, *GABRA5*, *GABRG3*) are among the nonimprinted genes and likely contribute to phenotypic features, especially the fast activity. The epileptic encephalopathy gene *GABRB3* likely contributes to epilepsy in these children [13,15].

Our study was limited by the retrospective data collection that prevented us from reviewing all sleep EEG records with a standardized protocol and scoring system or obtaining detailed phenotypic data near the time the EEG was obtained (e.g., recent clinical regression). We did not control for the potential effects of medication or comorbid disorders (e.g., mood or ADHD) due to our modest sample size.

5. Conclusion

This is the first report, to our knowledge, on unique sleep EEG patterns in children with Dup15q syndrome. The potential significance of these findings in cognitive function and epilepsy needs to be determined with larger follow-up studies.

Acknowledgments

All coauthors were substantially involved in the study and/or the preparation of the manuscript. No undisclosed groups or persons had a primary role in the study and/or manuscript preparation, and all coauthors reviewed and approved the submitted version of the paper and accept responsibility of its content. There was no funding associated with this manuscript.

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.

Disclosures of conflict of interest

Dimitrios Arkilo receives funding for investigational trials from UCB Pharma, GW pharmaceutical, and Pfizer. Okeanis Eleni Vaou is on the speaker's bureau for Impax and Teva pharmaceuticals. Shafali Jeste is a consultant for Roche pharmaceuticals. Jason Lerner is a consultant for Bristol-Myers Squibb. The remaining authors have no disclosures or conflicts of interest.

References

- [1] Battaglia A. The inv dup (15) or idic (15) syndrome (Tetrasomy 15q). *Orphanet J Rare Dis* 2008;19:3–30.
- [2] Chamberlain SJ, Lalande M. Neurodevelopmental disorders involving genomic imprinting at human chromosome 15q11-q13. *Neurobiol Dis* 2010;39(1):13–20.
- [3] Dennis NR, Veltman MW, Thompson R, Craig E, Bolton PF, Thomas NS. Clinical findings in 33 subjects with large supernumerary marker (15) chromosomes and 3 subjects with triplication of 15q11-q13. *Am J Med Genet A* 2006;140(5):434–41.
- [4] Conant KD, Finucane B, Cleary N, Martin A, Muss C, Delany M, et al. A survey of seizures and current treatments in 15q duplication syndrome. *Epilepsia* 2014; 55(3):396–402.
- [5] Buoni S, Sorrentino L, Farnetani MA, Pucci L, Fois A. The syndrome of inv dup (15): clinical, electroencephalographic and imaging findings. *J Child Neurol* 2000;15(6): 380–5.
- [6] Chifari R, Guerrini R, Pierluigi M, Cavani S, Sgro V, Elia M, et al. Mild generalized epilepsy and developmental disorder associated with large inv dup (15). *Epilepsia* 2002;43(9):1096–100.
- [7] Valente KD, Freitas A, Fridman C, Varela M, Silva AE, Fett AC, et al. Inv dup (15): is the electroclinical phenotype helpful for this challenging clinical diagnosis? *Clin Neurophysiol* 2006;117(4):803–9.
- [8] Cook Jr EH, Lindgren V, Leventhal BL, Courchesne R, Lincoln A, Shulman C, et al. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet* 1997;60(4):928–34.
- [9] Gurrieri F, Battaglia A, Torrisi L, Tancredi R, Cavallaro C, Sangiorgi E, et al. Pervasive developmental disorder and epilepsy due to maternally derived duplication of 15q11-q13. *Neurology* 1999;52(8):1694–7 [12].
- [10] Jaimcharyatam N, Rodriguez CL, Budur K. Prevalence and correlates of alpha delta sleep in major depressive disorders. *Innov Clin Neurosci* 2011;8(7):35–49.
- [11] Vijayan S, Klerman EB, Adler GK, Kopell NJ. Thalamic mechanisms underlying alpha-delta sleep with implications for fibromyalgia. *J Neurophysiol* 2015;114(3): 1923–30.
- [12] Sanchez Fernandez I, Chapman KE, Peters JM, Harini C, Rotenberg A, Lodenkemper T. Continuous spikes and waves during sleep: electroclinical presentation and suggestion for management. *Epilepsy Res Treat* 2013:583–531.
- [13] Paz JT, Davidson TJ, Frechette ES, Delord B, Parada I, Peng K, et al. Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. *Nat Neurosci* 2013;16(1):64–70.
- [14] Kim HJ, Kim HD, Lee JS, Heo K, Kim DS, Kang HC. Long-term prognosis of patients with Lennox–Gastaut syndrome in recent decades. *Epilepsy Res* 2015;110:10–9.
- [15] Epi4K Consortium; Epilepsy Phenome/Genome Project, Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, et al. De novo mutations in epileptic encephalopathies. *Nature* 2013;501(7466):217–21.