Clinical Neurophysiology 132 (2021) 1126–1137

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Electro-clinical features in epileptic children with chromosome 15q duplication syndrome

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ARTICLE INFO

Article history:
Accepted 22 February 2021
Available online 10 March 2021

Keywords:
15q11q13
Dup15q
Isodicentric chromosome 15q
Inv dup 15
Interstitial chromosome 15q
EEG

HIGHLIGHTS

- West or Lennox-Gastaut syndrome often occur in isodicentric chromosome 15q duplication.
- Focal epilepsy often occurs in interstitial chromosome 15q duplication.
- Chromosome 15q duplication displays abundant beta rhythms in wakefulness, decreasing in sleep.

ABSTRACT

Objective: We aimed to describe epilepsy and EEG patterns related to vigilance states and age, in chromosome15-long-arm-duplication-syndrome (dup15q) children with epilepsy, in both duplication types: interstitial (intdup15) and isodicentric (idic15).
Methods: Clinical data and 70 EEGs of 12 patients (5 intdup15, 7 idic15), followed from 4.5 m.o to 17y4m (median follow-up 8y3m), were retrospectively reviewed. EEGs were analyzed visually and using power spectrum analysis.
Results: Seventy video-EEGs were analyzed (1–16 per patient, median 6), follow-up lasting up to 8y10m (median 4y2m): 25 EEGs in intdup15 (8 m.o to 12y.o, median 4y6m) and 45 EEGs in idic15 (7 m.o to 12 y.o, median 15 m). Epilepsy: 6 West syndrome (WS) (2intdup15, 4idic15); 4 Lennox-Gastaut syndromes (LGS) (1 intdup15, 3 idic15), 2 evolving from WS; focal epilepsy (3 intdup15). In idic15, WS displayed additional myoclonic seizures (3), atypical (4) or no hypsarrhythmia (2) and posterior predominant spike and polyspike bursts (4). Beta-band rapid-rhythms (RR): present in 11 patients, power decreased during non-REM-sleep, localization shifted from diffuse to anterior, peak frequency increased with age.
Conclusion: WS with peculiar electro-clinical features and LGS, along with beta-band RR decreasing in non-REM-sleep and shifting from diffuse to anterior localization with age are recognizable

Abbreviations: ACTH, adrenocorticotropic hormone; ASD, autism spectrum disorder; ASM, anti-seizure medication; BP, breakpoint; BPF, beta peak frequency; DSA, density spectral array; dup15q, chromosome 15 long arm duplication; ECG, electrocardiogram; EMG, electromyography; ES, epileptic spasms; ESES, electrical status epilepticus during sleep; FISH, Fluorescence *In Situ* Hybridization; GTCS, generalized tonic-clonic seizures; GABR, gamma-aminobutyric acid type A receptor; HC, hydrocortisone; ID, intellectual disability; idic15, inversion-duplication of chromosome 15; intdup15, interstitial duplication of chromosome 15; INAD, infantile neuroaxonal dystrophy; LGS, Lennox-Gastaut syndrome; PSD, power spectral density; PWACR, Prader-Willi syndrome and Angelman syndrome critical region; RR, rapid rhythms; VGB, vigabatrin; WS, West syndrome.

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https://doi.org/10.1016/j.clinph.2021.02.010

features pointing towards dup15q diagnosis in children with autism spectrum disorder and developmental delay.
Significance: This study describes electroclinical features in both interstitial and isodicentric duplications of chromosome 15q, in epileptic children, including some recent extensions regarding sleep features; and illustrates how the temporo-spatial organization of beta oscillations can be of significant help in directing towards dup15q diagnosis hypothesis.

1. Introduction

Chromosome 15 long arm duplication (dup15q) involving the 15q11-q13 region is the most frequent copy number gain with complete penetrance associated with autism spectrum disorder (Moreno-De-Luca et al., 2013). The proximal region of the long arm of chromosome 15 (15q) is characterized by the presence of segmental duplications (or low copy repeats) (breakpoint 1 (BP1) to breakpoint 5 (BP5)) that facilitate recurrent illegitimate recombination and occurrence of chromosomal rearrangements (Stankiewicz and Lupski, 2002; Hogart et al., 2010) (Fig. 1). Paternally or maternally derived deletions of 15q11.2q13.1 region cause Prader-Willi syndrome (MIM # 176270) and Angelman syndrome (MIM # 105830) respectively. The Prader-Willi/Angelman critical region (PWACR) within 15q11.2q13.1 is located between BP2 and BP3 and is approximately 5 Mb in size (Finucane et al., 2016) (Fig. 1). Inversely, the diagnosis of dup15q is established by the detection of at least one extra maternally derived copy of the PWACR (Finucane et al., 2016).

In dup15q syndrome, two duplication types involving the PWACR exist. Firstly, interstitial 15q11.2q13.1 duplication (intdup15) (also named « partial 15q11q13 duplication » or « intrachromosomal 15q11q13 duplication ») (MIM # 608636) takes place within chromosome 15 and most often results in trisomy of PWACR (Roberts et al., 2002) (Supplementary Material); occasionally interstitial triplication can lead to tetrasomy of the same region. Secondly, isodicentric duplication (idic15) (Battaglia et al., 1997; Battaglia, 2008) (also named "supernumerary marker of chromosome 15" or "invdup15" standing for inversion-duplication of chromosome 15) results from two extra-copies of 15q11.2q13.1 ligated end-to-end as a supernumerary pseudo-dicentric chromosome with two centromeres (Mattei et al., 1984; Finucane et al., 2016), leading to tetrasomy of BP2-to-BP3 segment including the PWACR (Supplementary Material). Both intdup15 and idic15 are maternally derived (Finucane et al., 2016; Roberts et al., 2003). Due to the presence of imprinted genes within the PWACR, trisomy and tetrasomy of maternal origin are known to be pathogenic (Dittrich et al., 1996; Mohandas et al., 1999; Bolton et al., 2001; Finucane et al., 2016); whereas paternally derived copy number gains are typically associated with more variable neurodevelopmental phenotypes (Cook et al., 1997; Urraca et al., 2013). The PWACR also encompasses non-imprinted genes such as three gamma-aminobutyric acid type A receptor (GABR) subunits genes: *GABRA5*, *GABRB3*, and *GABRG3*, which are associated with epilepsy (Benarroch, 2007) (Fig. 1).

Clinical presentation in dup15q includes hypotonia, developmental delay, intellectual disability (ID), autism spectrum disorder (ASD) and epilepsy (Battaglia et al., 1997; Bolton et al., 2001; Dennis et al., 2006; Battaglia, 2008; Finucane et al., 2016). Clinical evolution is correlated to duplication type with a more severe phenotype in idic15 patients (Battaglia et al., 2010; Hogart et al., 2010; Urraca et al., 2013; Al Ageeli et al., 2014; Conant et al., 2014; Finucane et al., 2016; Matricardi et al., 2018). Epilepsy is reported in approximately 25% of intdup15 patients and 65% of idic15 patients (Conant et al., 2014; Finucane et al., 2016). It is of early-onset and treatment-refractory in idic15, with multiple seizure types including epileptic spasms (ES), tonic-clonic, tonic, myoclonic, atonic, and focal-onset seizures along with absences (Conant et al., 2014). Idic15 patients sometimes evolve towards Lennox-Gastaut syndrome (LGS) (Valente et al., 2006; Battaglia, 2008; Orrico et al., 2009).

EEG features have been described in children and adults (Battaglia et al., 1997; Cook et al., 1997; Buoni et al., 2000; Chifari et al., 2002; Valente et al., 2006; Battaglia, 2008; Urraca et al., 2013; Arkilo et al., 2016; Matricardi et al., 2018). However, unusual beta activity has been reported upon visual analysis (Bahi-Buisson et al., 2005; Urraca et al., 2013; Al Ageeli et al., 2014) and has been recently quantified as excessive in dup15q patients in comparison with autistic age-and-IQ-matched children and to healthy typically developing age-matched children, regardless of duplication type (Frohlich et al., 2016), thus raising the question of the critical role possibly played by enhanced GABAergic transmission (Frohlich et al., 2019) in this phenotype.

Although clinical genotype-phenotype correlations have been studied, longitudinal electro-clinical features including temporal

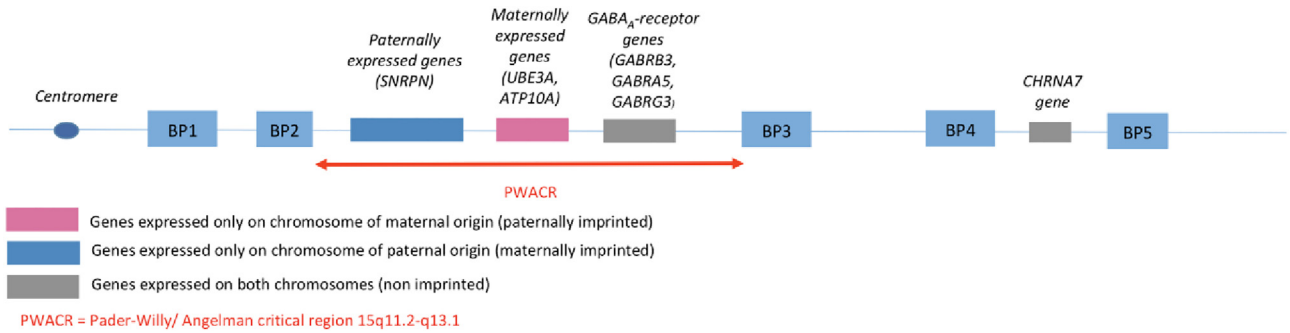

Fig. 1. Prader-Willy/Angelman critical region (PWACR) expression map within chromosomal region 15q11.2q13.1. BP = breakpoint, GABR = gamma-aminobutyric acid type A receptor.

and spatial evolution of EEG rhythms depending on vigilance states and ageing are needed. Our aim was to describe seizure types and epilepsy and to characterize ictal and interictal EEG patterns as well as their evolution with vigilance states and age, in children with dup15q and epilepsy.

2. Methods

2.1. Subjects

Among the patients presenting dup15q syndrome followed in the departments of pediatric neurology and genetics at Necker-Enfants-Malades Hospital, we included those who had undergone one or more polygraphic video-EEG recordings between October 2007 and July 2019.

2.2. Ethics

The study received the approval of CENEM ethics committee of Necker-Enfants-Malades Hospital and was listed in the general registry of data treatment of Assistance-Publique-des Hôpitaux-de-Paris (APHP) under the registration number 2020 0130112345. Informed consent for genetic testing was obtained from all tested patients and their relatives.

2.3. Clinical investigation

We retrospectively reviewed clinical data available in the patient's medical record regarding personal and family history, pregnancy, birth, development, behavior, ASD, age at seizure onset, seizure type or seizure semiology, epilepsy syndrome when applicable and anti-seizure medication (ASM).

2.4. Genetic analysis

For patients A to C and G to L, Agilent CGH microarray 60 K (Agilent Technologies, Santa Clara, CA) was used for genomic copy number analyses that were carried out according to manufacturer's recommendations. Using standard protocols, chromosomal rearrangements were confirmed by Fluorescence *In Situ* Hybridization (FISH) with the BACs (Bacterial Artificial Chromosome) on chromosomes preparations from leukocyte cultures. Parental testing was performed with the same probes. Genomic positions are relative to human genome Build NCBI37/hg19. For patients D, E and F, chromosome karyotype analysis was performed on peripheral blood lymphocytes with standard G-banding and R-banding.

2.5. EEG

We retrospectively reviewed video-EEG recordings available in Necker-Enfants-Malades Hospital EEG database for dup15q-diagnosed patients. Video-EEG-recordings included polygraphic parameters as electrocardiogram (ECG), respiration and surface electromyography (EMG). The number of electrodes (silver chloride cup electrodes) ranged from 9 to 21, and electrodes were placed according to the 10/20 international system using the medial frontal polar (FPz) as reference. EMG was recorded with two cup electrodes placed 2 cm apart on deltoid muscles. Recordings lasted at least one hour up to 24 hours, always including wake and sleep periods. Signals were amplified (x1000), bandpass filtered at 0.01–97 Hz and digitized at 256 Hz, using the Deltamed Coherence EEG system (Deltamed/Natus® Paris, France).

2.5.1. Visual analysis

Polygraphic EEG-video recordings were analyzed visually. We characterized background activity in awake and sleep states, interictal epileptiform abnormalities and - if recorded - seizure types. We characterized the EEG rhythms according to vigilance states (in wakefulness, drowsiness and sleep), their spatial organization along 10 electrodes (frontal Fp1-Fp2, central C3-C4, anterior temporal F7-F8, temporal T5-T6 and occipital O1-O2) by using density spectral array (DSA) as well as spectral analysis of the Coherence EEG system (Deltamed/Natus® Paris, France). For each EEG recording, we performed multi-track DSA spectral analysis, with 4 seconds per page resolution and a frequency scale of 1 to 48 Hz and applied the spectral mono-track analysis that provided the predominant frequency and peak-to-peak amplitude of RR.

2.5.2. Spectral analysis

As ages at EEG were not equally distributed among the whole population of patients, four age groups (<1y.o, 1–2 y.o, 2–6 y.o, >6 y.o) were chosen in order to assess EEG maturation and to allow a maximum number of participants in each group. Although several EEGs were available in some patients, we did use only one EEG per patient and per age-group, in order to avoid statistical confounds and weighting bias. We thus selected for each patient the EEG-recording with the best quality and containing as many vigilance states as possible (wake, drowsiness, sleep and awakening). Applying the Welch method (Welch, 1967), we quantified and mapped spectral FFT power in each of the usual EEG frequency bands: delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–48 Hz). The EEG-recording selections contained at least three minutes in different vigilance states. Preprocessing and analysis of EEG signals were realized with MNE Python (Gramfort et al., 2014) and Autoreject (Jas et al., 2016) following a method previously validated (Lefebvre et al., 2018). For each patient, we extracted the power spectral density (PSD; in dB) during the wake and sleep states. Then we compared PSD between wake and sleep for each electrode (Fp1, Fp2, F7, F8, C3, C4, T5, T6, O1, O2; Bonferroni-corrected across the 10 electrodes). None of the EEGs included for PSD analysis was from patients under benzodiazepine medication.

3. Results

Twelve patients (8 males, 4 females) were included. They were followed from age 4.5 m.o to 17y4m. Follow-up duration was 18 m to 12y8m (median 8y3m).

3.1. Genetics

Five patients had intdup15 and seven had idic15. In all patients, the region between BP2 and BP3, including GABR-genes cluster, was duplicated. Among available genetic transmission (7/12), rearrangements were either de novo (5/7) or maternally derived (2/7), none was paternally derived (for detailed genetic data, see Table 1).

3.2. Clinics

At last clinical follow-up, patients were between 9y6m to 17y4m (median 12y9m) in intdup15 group, and between 2y2m to 12 y.o (median 6y8m) in idic15 group. None of their parents were related. All patients underwent normal pregnancy and uneventful delivery. In all patients, fixed psychomotor delay and autistic features were observed. No dysmorphic features were reported. MRI, when available (9/12), did not disclose any specific cerebral abnormality (for detailed clinical data, see Table 2).

Table 1
Genetic characteristics of patients.

Patient	Sex	Genetics	Genomic coordinates (genome assembly GRCh37 (hg19)) / Karyotype +/- FISH	Copy number gain	PWACR BP2-BP3 copies
A	M	Intdup15	arr [GRCh37] 15q11.2q13.1(20335887_27000753)x3 dn	BP1-BP3 (3 copies)	3
B*	M		arr [GRCh37] 15q11.2q13.1(22784523_28525460)x3 mat	BP1-BP3 (3 copies)	3
C*	M		arr [GRCh37] 15q11.2q13.1 (22980072_28525460)x3 mat	BP1-BP3 (3 copies)	3
D	F		46,XX.ish dup(15)(q12q12)(RP11-1081A4++,RP11-641C16++)	*n.a* (at least 3 copies (BP2-BP3))	3
E	F		arr [GRCh37] 15q11.2q13.1 (22873688_23179948x3,23699701_28525460x4)	BP1-BP2 (3 copies), BP2-BP3 (4 copies)	4
F	M	Idic 15 *n.a*	47, XY,+idic(15)(pter→q13::q13→pter)	*n.a* (at least 4 copies (BP2-BP3))	4
G	F	sym	arr [GRCh37] 15q11.2q13.1 (21939652_28525460)x4	cen-BP3 (4 copies)	4
H	M	sym	arr [GRCh37] 15q11.2q13.1 (20102541_28525460)x4	cen-BP3 (4 copies)	4
I	M	sym	arr [GRCh37] 15q11.2q13.1 (20102541_28525460)x4 dn	cen-BP3 (4 copies)	4
J	M	asym	arr [GRCh37] 15q11.1q13.3 (22784523_30322079x4,30322079_32438943x3)dn	cen-BP4 (4 copies), BP4-BP5 (3 copies)	4
K	F	asym	arr [GRCh37] 15q11.1q13.3 (20102541_30322079x4,30322079_32510863x3)dn	cen-BP4 (4 copies), BP4-BP5 (3 copies)	4
L	M	asym	arr [GRCh37] 15q11.1q13.3 (20102541_31234158x4,31234158_32510863x3)dn	cen-BP4 (4 copies), BP4-BP5 (3 copies)	4

* Siblings (same mother). Note the maternal imprinting: patients B and C had inherited the duplication from the same carrier mother (with different fathers), who was inversely not clinically affected presumably having paternal imprinting of her own duplication (but further genetic data of grandparents were not available in this study). asym: asymmetrical, BP: breakpoint, cen: centromere, dn: *de novo*, idic15: inversion-duplication of chromosome 15, intdup15: interstitial duplication of chromosome 15, mat: maternally derived, *n.a*: non available, PWACR: Prader-Willi syndrome and Angelman syndrome critical region, sym: symmetrical.

3.2.1. Seizure types and epileptic syndromes

Epilepsy started between 4.5 m.o and 10yrs (median 9 m.o) in intdup15 patients; between 5 m.o and 8yrs (median 8 m.o) in idic15 patients. Seizures (recorded or reported, see Table 2) consisted in epileptic spasms (ES) in 7 patients (2/5 intdup15; 5/7 idic15), tonic seizures in 7 patients (2/5 intdup15; 5/7 idic15), myoclonic seizures in 4 patients (1/5 intdup15; 3/7 idic15), atypical absence seizures in 4 patients (1/5 intdup15; 3/5 idic15), focal seizures (frontal, parieto-temporal, occipital) in 4 patients (3/5 intdup15; 1/7 idic15), and generalized tonic-clonic seizures (GTCS) in 6 patients (2/5 intdup15; 4/7 idic15). ES were symmetric without any associated focal sign, occurring in clusters or isolated. In three patients, all in the idic15 group, ES and myoclonic seizures were recorded at the same time period, sometimes within the same cluster. In two idic15 patients, clusters of myoclonias were triggered during intermittent photic stimulation at 1 Hz and between 1 to 60 Hz, at the age of 8 and 15 months respectively.

Epilepsy type was classified as focal in 3 patients, all in intdup15 group (3/5). West syndrome was observed in 6 patients (2/5 intdup15, 4/7 idic15), Lennox-Gastaut syndrome in 4 patients (1/5 intdup15; 3/5 idic15) with two (1 intdup15 and 1 idic15) evolving from West syndrome. In one patient, epilepsy could not be classified: at 13 m.o he developed ES without asymmetry and without psychomotor regression along with stereotyped focal seizures, myoclonic seizures and GTCS. ES ceased at 2y3m. Myoclonic seizures, tonic seizures, GTCS and focal seizures persisted at last follow-up at 6y8m, however lacking electroclinical criteria of LGS.

3.2.2. Antiseizure medication and response to ASMs

At last follow-up, half of the patients were seizure-free (4/5 intdup15, 2/7 idic15), three of them on monotherapy, three under two ASMs. Six patients had persistent seizures, of whom four patients presented with LGS: three under polytherapy and one not taking any ASM by his parents' choice. In all 6 patients diagnosed with WS, ES ceased by the age of 12 m.o. Four of them had received VGB, but ES were refractory to VGB in monotherapy. ES stopped when VGB was associated with Topiramate (1/4) or Hydrocortisone (3/4). Patients with focal epilepsy in intdup15 group became seizure-free under Topiramate, Levetiracetam or Lamotrigin and Carbamazepine in association, respectively (see Table 2).

3.3. EEG

3.3.1. Visual analysis

Seventy video-EEGs were analyzed (1–16 EEGs per patient, median 6): 25 EEGs in intdup15 group (from 8 m.o to 12y.o, median 4y6m) and 45 EEGs in idic15 group (from 7 m.o to 12 y.o, median 15 m), with a follow-up period lasting up to 8y10m (median 4y2m) (Table 2).

During wake, posterior dominant rhythm was visible in 9/12 patients by the age of 2y8m (all patients but B, F, I), although remaining slow for age in 6/9. The other 3 patients never developed anterior-posterior spatial organization, and their EEG displayed generalized or multifocal spikes, spike-and waves or polyspikes. During sleep, physiological figures such as sleep spindles were visible in 8/12 patients and appeared at the latest by the age of 2y.o. The four remaining patients displayed neither sleep spindles nor vertex sharp waves by the age of 4y2m to 12 y.o respectively.

In the 6 patients with WS, hypsarrhythmia was atypical in four (2 intdup15, 2 idic15) and absent in 2 (idic15). Hypsarrhythmia was termed atypical because amplitude increase was moderate, allowing interpretation at usual sensitivity, and slowing of the background was also moderate with the presence of theta activities. Interictal paroxysmal EEG abnormalities were transiently pre-

Table 2a
Electro-clinical characteristics of patients: interstitial duplication of chromosome 15 (intdup15) group.

ID	Sex	Age at first clinical follow-up	Age at last clinical follow-up	Age at seizure onset	Seizure type(s)		EEG features	EEG follow-up [age at first; age at last] N= number available	Epilepsy type/syndrome	Epilepsy outcome	Neurological development	ASMs (chronological order)
					Recorded	Other reported						
A	M	20m.o	11 y4m	6 m.o	ES	none	Atypical hyps.	1y9m [1y6; 3y5m] N=3	WS	Seizure free at 7m.o (VGB+HC)	AD, walking, poor language	VGB + HC, VGB
B*	M	4y8m	17 y4m	9 m.o	ES->3 y.o: GTCS, TS, MS, AA	none	Atypical hyps.	4y2m [4y9; 8y11m] N=2	WS --> LGS	Persistent GTCS (2-3 clusters/month, up to 5 seizures/cluster)	AD (stereotypies), standing, no language	VPA + LTG + CLB + KD and callosotomy and vagal nerve stimulation
C*	M	10m.o	9y6m	4.5 m.o	none	Focal motor (asymmetrical tonic spasms/frontal seizures, nocturnal hypermotor events)	Normal at 3m.o Right occipital and left central spikes at 3y.o Subnormal, no spikes at 9y.o	8y10m [8m; 9y6m] N=6	Focal epilepsy	Seizure free at 9y5m: Focal seizures ceased at 9m.o (VPA+VGB). Seizure free interval until 9y.o. Frontal seizures ceased at 9y5m (TPM)	AD, walking, moderate language delay	VPA, VPA+VGB, TPM
D	F	3y2m	13y	4 y.o	Left occipital subclinical seizure (4yrs)	Focal seizures with eye deviation, episodes of LoC	Occipital spikes	6y4m [2y8m; 9y] N=7	Focal epilepsy	Seizure free at 4y.o (LVT)	AD, walking, good language, moderate learning difficulties	LTG, LVT
E	F	2y4m	12y9m	10 y.o	Left parieto-temporal seizure with behavioral arrest and partial LoC (11yrs)	Focal to bilateral tonic clonic seizures (GTCS), TS, episodes of LoC	Bilateral fronto-temporal spikes	8y [2y; 12y] N=7	Focal epilepsy	Seizure free at 11y.o (LTG+CBZ)	AD, walking, no language	LTG+CBZ

AA: atypical absence seizures, AD: autistic disorder features, ASM: antiseizure medication, CBZ: carbamazepine, CLB: clobazam, CLZ: clonazepam, ES: epileptic spasms, GTCS: generalized tonic-clonic seizures, HC: hydrocortisone, hyps. : hypsarrhythmia, IPS intermittent photic stimulation, KD : ketogenic diet, LGS: Lennox Gastaut syndrome, LTG: lamotrigin, LoC: loss of consciousness, LVT : levetiracetam, MS: myoclonic seizures, RFN : rufinamide, TPM: topiramate, TS: tonic seizures, VGB : vigabatrin, VPA: sodium valproate, WS: West syndrome, ZNS : zonisamide. *n.a*: non available.

Table 2b
Electro-clinical characteristics of patients: isodicentric duplication of chromosome 15 (idic15) group..

ID	Sex	Age at first clinical follow-up	Age at last clinical follow-up	Age at seizure onset	Seizure type(s) Recorded	Seizure type(s) Other reported	EEG features	EEG follow-up [age at first; age at last] N= number available	Epilepsy type/syndrome	Epilepsy outcome	Neurological development	ASMs (chronological order)
F	M	12y.o	12 y.o	5 y.o	AA, TS, GTCS (12yrs)	none	Frontal predominant spike and waves, polyspikes in sleep	once [12y] N=1	LGS	Persistent TS, AA, GTCS (several per day)	AD, walking, no language	VPA, VPA + LVT+ LTG, VPA + TPM+ LTG, HC+ TPM+ LTG+ VPA, CBZ+ LTG+ VPA, RFN+ CBZ+ LTG+ VPA, RFN + CBZ+ LTG+ VPA + CLZ, RFN + CBZ+ LTG+ VPA + CLZ + KD, CBZ+ LTG+ KD, (VPA+ LTG+ KD: unknown outcome)
G	F	7 m.o	2y6m	7 m.o	ES, TS in clusters, MS mainly in sleep MS on IPS at 15m.o disappearing at 2y6m	none	Atypical hyps. Posterior spikes and spike/polyspike bursts	12m [7m, 1y7m] N=8	WS	ES + atypical hyps. ceased at 9 m.o (VGB+HC). Persistent MS	Sitting, intermittent eye contact	VGB, VGB + HC, VGB
H	M	8 m.o	2y2m	8 m.o	ES in clusters MS (without constant EEG correlate)	none	Atypical hyps. Posterior spikes and spike/polyspike bursts (ceased after HC therapy)	10m [8m; 1y6m] N=6	WS	Seizure free at 9m.o (VGB + HC)	No sitting, intermittent eye contact	VGB, VGB + HC, VGB
I	M	9 m.o	6y8m	13 m.o	MS at 13m.o, ES, focal (occipital) seizures	TS, GTCS, episodes of oculoclonia without LoC	No hyps. at 13 m.o, Rare interictal temporo-occipital spikes	3y1m [1y1m;4y2m] N=4	Unclassifiable	ES/TS ceased at 2y3m (LVT). Persistent GTCS and focal seizures (1-2 per week)	AD (stereotypies), standing, no eye contact	LVT, LVT+ CLB, ZNS, ZNS + LVT, ZNS + VPA
J	M	8 m.o	8y10m	8 y.o	none	GTCS, drop attacks, absences	Right and left temporo-occipital spikes/polyspikes Diffuse polyspikes and spike-waves in sleep	7y4m [1y6;8y11m] N=4	LGS	Persistent seizures (free intervals of 1 week, up to 2 seizures/day)	AD, walking, moderate language delay	None (parents refusal)
K	F	8 m.o	2y2m	7 m.o	ES, TS in clusters	none	No hyps. Posterior spikes and spike/polyspike bursts/sequences	1y9m [7m; 2y2m] N= 6	WS	Seizure free at 9 m.o	Sitting, good eye contact, stereotyped activities, poor language	LVT, VPA
L	M	8 m.o	7y2m	5 m.o	ES and TS in clusters, bilateral clonic seizures on IPS at 8 m.o. AA, TS, subclinical long lasting bi-central spike-wave discharges at 2y9m	GTCS	No hyps. Posterior spikes and spike/polyspike bursts at 8 m.o; Diffuse polyspikes at 2y9m Rare centro-parietal spikes at 6y.o	5y8m [8m;6y4m] N= 16	WS --> LGS	Persistent brief TS and GTCS (1/month)	AD (stereotypies), walking, no language	VGB, VGB+TPM, CLZ+ VGB+ TPM, VGB+ VPA+ CLZ+ ZNS + KD, TPM+RFN+ VPA + KD, VPA+ RFN + KD

AA: atypical absence seizures, AD: autistic disorder features, ASM: antiseizure medication, CBZ: carbamazepine, CLB: clobazam, CLZ: clonazepam, ES: epileptic spasms, GTCS: generalized tonic-clonic seizures, HC: hydrocortisone, hyps.: hypsarrhythmia, IPS intermittent photic stimulation, KD: ketogenic diet, LGS: Lennox Gastaut syndrome, LTG: lamotrigin, LoC: loss of consciousness, LVT: levetiracetam, MS: myoclonic seizures, RFN: rufinamide, TPM: topiramate, TS: tonic seizures, VGB: vigabatrin, VPA: sodium valproate, WS: West syndrome, ZNS: zonisamide. *n.a*: non available.

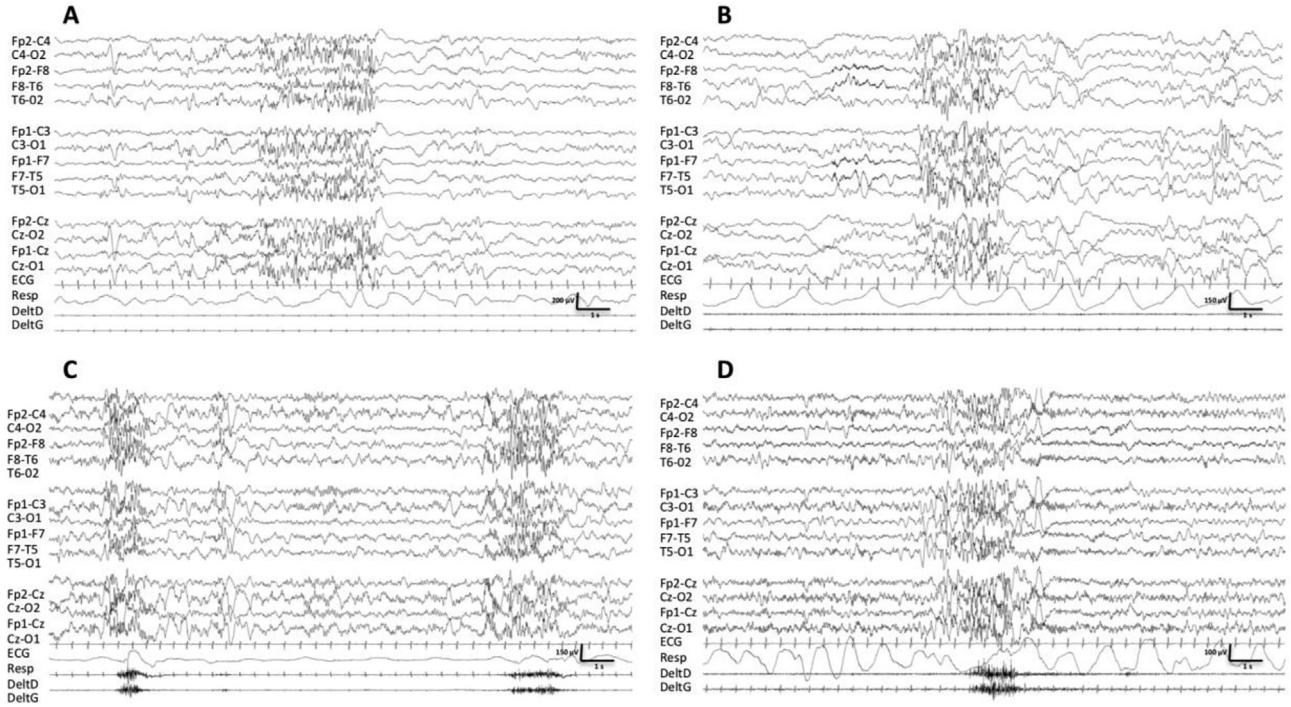

Fig. 2. Posterior predominant spike/polyspike bursts. A) Patient G, 7 m.o, drowsiness, no drug treatment. No motor manifestation. B) Patient H, 8 m.o, drowsiness, no drug treatment. No motor manifestation. C) Patient K, 7 m.o, sleep, under levetiracetam. Concomitant with subtle brief tonic contraction of upper limbs. D) Patient L, 8 m.o, wakefulness, under vigabatrin. Concomitant with subtle brief tonic contraction of upper limbs.

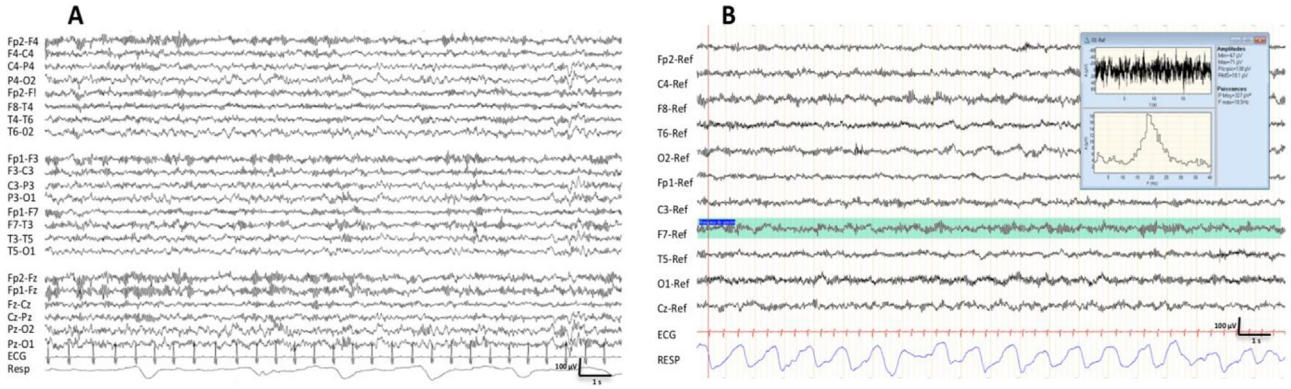

Fig. 3. Patient C, 9y6m under topiramate. A) Anterior predominance (Fp1, Fp2) of rapid rhythms in spectral analysis and raw EEG in the awake state. B) Semi-quantitative analysis showing beta-peak frequency at 20 Hz on selected lead F7.

sent in all patients and in both groups. They consisted of monofocal, multifocal or bilateral synchronous spikes, polyspikes or spike-wave bursts or sequences. In 4 of the 6 patients with WS, all idic15 (patients G, H, K, L), a highly similar pattern was observed at the beginning of the seizures (age 7–8 months) consisting in diffuse with posterior predominance spikes and spike/polyspike bursts (Fig. 2a, b).

Ictal EEG was typical in ES showing diffuse high voltage slow complexes associated with fast activities, in myoclonic seizures (segmental or axial) diffuse spikes or spike waves. However, it is noteworthy that 4 patients with WS also presented brief tonic seizures (3–5 seconds), occurring in long-lasting series and with EEG correlate consisting in posterior predominant spike or polyspike bursts/sequences resembling the above mentioned interictal pattern (Fig. 2c, d).

On visual EEG signal and DSA spectral analysis, 11/12 patients showed abundant diffuse RR in the beta frequency range at all ages and in both duplication types (Fig. 3). Mean frequency beta-peak was at 20.1 Hz (ranging from 13 to 28.5 Hz). Mean peak-to-peak amplitude was 116 μV (ranging from 47 to 256 μV). They were present in wakefulness (11/11) and their power reduced during non-REM sleep (11/11) (Fig. 4). The excessive beta activity was neither modified by eye-opening/closure, nor by intermittent photic stimulation. Patient B (intdup15) was the only patient in whom RR could not be identified.

3.3.2. Spectral analysis

We respectively compared the power spectrum between wake and sleep states in the four previously described age groups (5 patients < 1 y.o, 7 patients 1–2 y.o, 5 patients 2–6 y.o and 6 patients > 6 y.o) (Fig. 5). All age groups showed an increase of power in the beta band during wake state when compared to sleep (Fig. 5**, line 1**). In group < 1 y.o, this difference did not reach significance after Bonferroni correction. The topography of beta

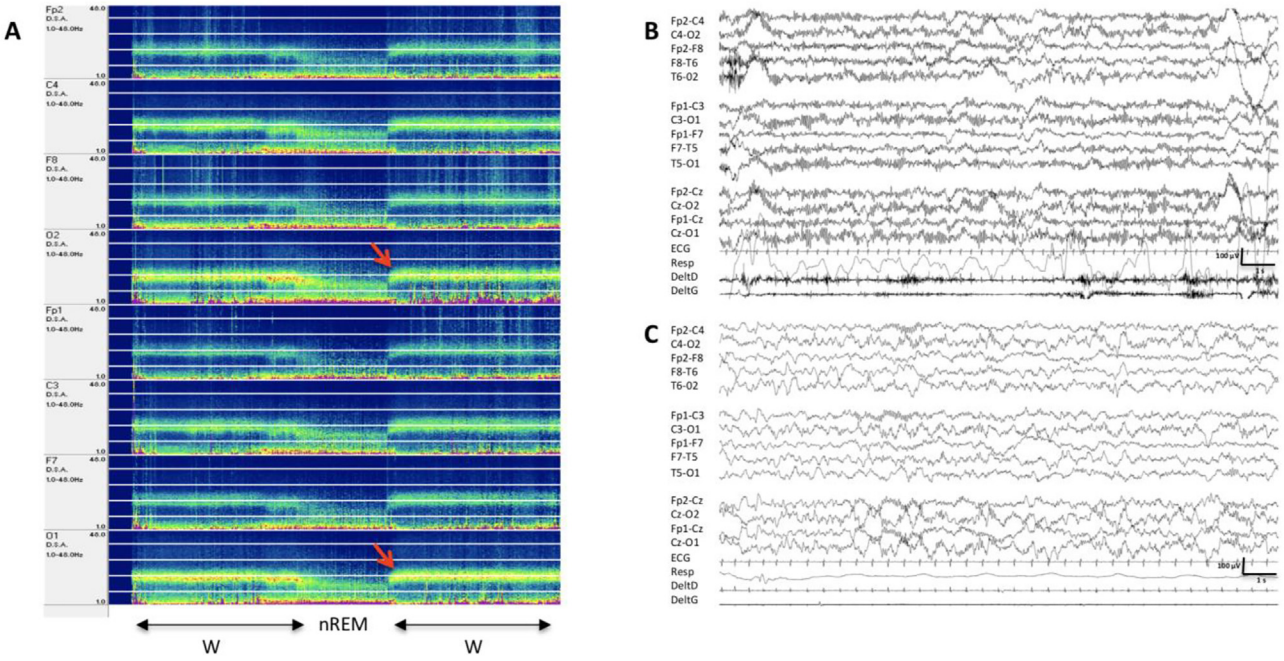

Fig. 4. Patient K, 7 m.o under levetiracetam. A) DSA (density spectral array) 1–48 Hz of selected electrodes (Fp2, C4, F8, O2, Fp1, C3, F7, O1) of 2.5 hours recording. Diffuse rapid rhythms at 20 Hz in wakefulness with occipital predominance (see increased spectral power on O2 and O1), and changes according to vigilance states (rapid rhythms (RR) present during wakefulness (W), decreased in frequency and power in non-REM sleep (nREM) and reappearing at awakening (red arrow). B) Wakefulness. C) Sleep; see sleep spindles.

power activity during wake compared to sleep appeared to be diffuse in the group [1–2 y.o], with fronto-temporal predominance in [2–6 y.o] and more localized on frontal electrodes in [>6 y.o] (Fig. 5**, line 3**). Mean beta peak frequency (BPF) increased with ageing during wakefulness from ~ 17 Hz to 27 Hz (Fig. 5**, line 1**). Intensification in beta-band RR during drowsiness, as suspected by visual DSA analysis, was not confirmed using power spectrum analysis. In patients < 2 y.o, during sleep, the spectral analysis also disclosed a significant increase in alpha rhythms at 8–11 Hz on central electrodes. In order to determine if this increase could be attributed to spindles, we specifically extracted spindle bursts from EEGs, when present, in patients < 2 y.o (5 patients < 1 y.o, 7 patients 1–2 y.o) and noticed that spindle frequency was at 14–15 Hz. Therefore, we inferred that before the age of two years, there was a significant rise in alpha rhythms during sleep compared to wakefulness, not explained by spindle activity.

4. Discussion

In our study including 12 patients with dup15q syndrome (intdup15 and idic15) and epilepsy, we describe epilepsy, seizure types as well as EEG rhythms in wakefulness and sleep, over a twelve-year period of time. To our knowledge, it is the largest longitudinal clinical study and age-related analysis of wake and sleep EEGs, in epileptic children with dup15q in both duplication types.

The main epileptic syndromes observed in our patients were WS and LGS, two epileptic encephalopathies caused by a very large spectrum of underlying etiologies. Among their genetic causes, dup15q chromosomal rearrangement had first been described by Battaglia et al. (Battaglia et al., 1997; Battaglia, 2008). It is noteworthy that in the six patients with WS, hypsarrhythmia was atypical in four and absent in two. In four idic15 children, EEGs showed a highly similar pattern of diffuse with posterior predominance spikes and spike/polyspike bursts. These bursts could occur in clusters and were then associated with brief tonic contractions. In most patients with WS, ES and myoclonic seizures were recorded at the same time period as previously reported by Matricardi et al. (Matricardi et al., 2018), sometimes within the same cluster. In *Conant's* series (Conant et al., 2014), WS was more frequently observed in idic15 compared to intdup15 patients. In our group, 2/5 indup15 and 4/7 idic15 patients presented with WS but our sample size was not large enough to delineate a significant trend. In our study group, LGS occurred in 2 patients de novo and in 2 patients after evolution from WS. One of these patients with LGS evolving from WS had intup15, a novel observation, since all reported cases of LGS or LGS-like syndrome in dup15q had idic15 (Valente et al., 2006; Rocha et al., 2012; Conant et al., 2014; Battaglia et al., 2016; Matricardi et al., 2018). The main epilepsy type in our intdup15 patients was focal epilepsy. Nevertheless, epilepsy syndromes in our patients might be more severe than the true phenotype range, owing to our recruitment as a tertiary referring center.

As previously reported (Conant et al., 2014; Matricardi et al., 2018) our patients presented with epileptic spasms, tonic seizures, myoclonic seizures, atypical absence seizures, focal seizures and GTCS. However, neither status epilepticus nor atonic seizures were observed in our series. In *Conant's* series (Conant et al., 2014), ES were more frequently observed in idic15 patients than in intdup15 ones. In our group, 2/5 intdup15 and 5/7 idic15 patients presented with ES but our sample size was not large enough to delineate a significant trend. *Battaglia* reported "several daily episodes of bizarre paroxysmal phenomena" with hypermotor semiology in one idic15 patient (Battaglia et al., 2016). Similar frontal seizure semiology occurred during sleep in one of our patients, who conversely displayed intdup15.

Regarding ASM, it has been suggested that $GABA_A$-receptor agonists (such as VGB or benzodiazepines) were associated with poor response in idic15 patients with ES; and for patients with idic15 and ES, the association ACTH/prednisone was superior to VGB in

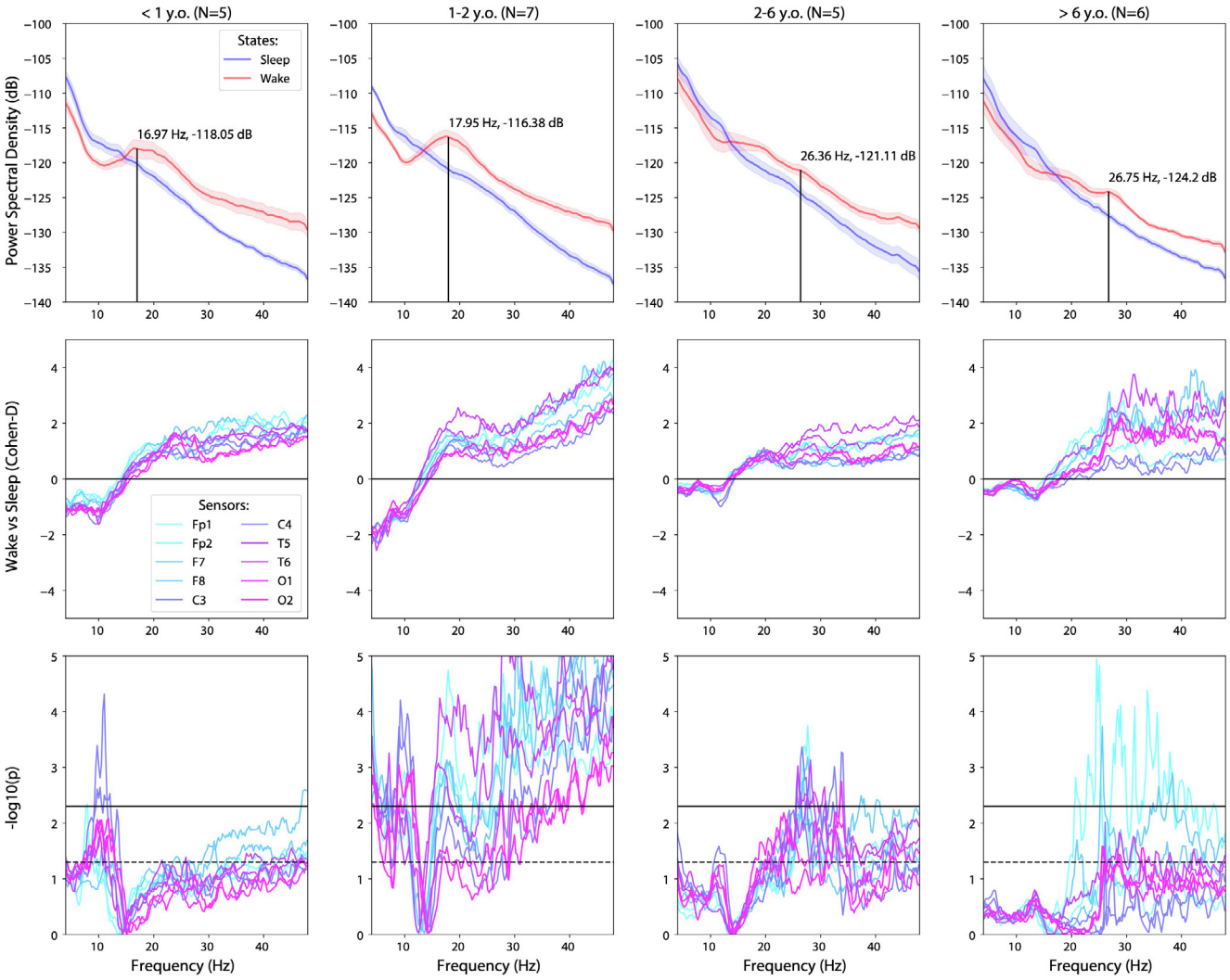

Fig. 5. Modulation of the EEG power spectrum between wake and sleep states. Group < 1 y.o: patients C, G, H, K, L (n = 5); Group 1–2 y.o: patients A, G, H, I, J, K, L (n = 7). Group 2–6 y.o: patients A, B, C, D, J (n = 5); Group > 6 y.o: patients B, C, D, E, F, J (n = 6). Line 1: Power spectral density (dB) during wake (red) and sleep (blue). Note the increase of power in the beta (13–30 Hz) and gamma (30–48 Hz) bands during wakefulness (red bumps indicated with the vertical black line). Line 2: Cohen's D effect size of the difference of power between wake and sleep for each sensor across frequency. Positive and negative values indicate respectively more power in wake and sleep. Line 3: P-value statistical significance of the difference of power between wake and sleep for each sensor across frequency. Dashed lines and plain lines indicate respectively nominal ($p < 0.05$) and Bonferroni-corrected ($p < 0.05/10$) significance thresholds. Note the appearance of significant diffuse beta band activity after 1 y.o, later switching to an anterior localization.

monotherapy (Conant et al., 2014). It is noteworthy that in our series, patients presenting with WS also rarely responded to VGB in monotherapy (1/5 intdup15, 0/7 idic15), which might suggest its lack of efficiency, as already pinpointed by *Matricardi et al.* (Matricardi et al., 2018); whereas, in all our patients with WS treated with hydrocortisone, atypical hypsarrhythmia promptly resolved. In *Battaglia*'s series of 35 idic15 patients, nine patients presented with WS, among them eight received high dose steroids (four of them had received Vigabatrin before) and hypsarrhythmia resolved in all. Half of these eight patients stayed seizure-free; however, three developed Lennox-Gastaut or Lennox-Gastaut-like syndrome and one generalized epilepsy (Battaglia et al., 2016). Interestingly, in one of our patients evolving from WS to LGS, posterior dominant rhythm - although slow for the age - first appeared when VGB was discontinued (at that time, the patient was under three other anti-seizure drugs and on a ketogenic diet), suggesting that suspending GABA-agonist medication might have contributed to improve EEG background activity. As little evidence exists regarding response to ASM (Conant et al., 2014; Battaglia et al., 2016), larger series of epileptic dup15q patients are necessary to evaluate the most appropriate treatment according to dup15q type.

Regarding interictal EEG features Battaglia et al. first described EEG features in 2 children and 2 adult idic15 patients as being non-specific (Battaglia et al., 1997; Battaglia, 2008). Chifari et al. reported in 2 idic15 patients regular background activity, generalized rhythmic spike-and-wave complexes at 3.5–4 Hz lasting 4-6secs (Chifari et al., 2002). Valente et al. (Valente et al., 2006) described 5 individuals with dup15q syndrome in which epilepsy type and EEG features could not point towards dup15q diagnosis. However, more recently, Battaglia (Battaglia et al., 2016) described as a characteristic interictal EEG a « considerable excess of fast activity at 12–20 Hz, reaching up to 200 µV, over both fronto-centro-temporal areas, particularly observed during childhood ». This EEG pattern had also been noticed in prior studies both in intdup15 and in idic15 patient's (Urraca et al., 2013; Al Ageeli

et al., 2014; Frohlich et al., 2016). *Frohlich et al.* recently quantified these RR by power spectrum analysis and showed that in patients with dup15q syndrome, beta power was significantly higher compared to autistic age-and-IQ-matched children and to healthy typically developing age-matched children (Frohlich et al., 2016) with stronger beta2 power (20–30 Hz) in participants with dup15q syndrome who did not have epilepsy. However, EEGs were recorded exclusively in the awake state, and most of the participants were non-epileptic.

In our series of dup15q patients with epilepsy, power spectrum analysis confirmed previous findings in the literature that RR were present in wakefulness. Their power significantly decreased during non-REM sleep, which has never been reported before and could help in guiding differential diagnosis. We noticed that in the group < 1y.o, this decrease of RR in sleep was not significant after Bonferroni correction, possibly due to atypical hypsarrhythmia present in 2/5 patients in this age group. Reports on sleep EEG in dup15q patients are rare. Arkilo et al. (Arkilo et al., 2016) described 3 different sleep patterns in 42 dup15q children: alpha-delta activity (9 idic15, 5 intdup15), electrical status epilepticus during sleep (ESES) in 15 patients (all idic15) and bursts of high amplitude bifrontal predominant paroxysmal fast activity during early stages of non-REM sleep in 15 children (14/15 idic15, all with drug-resistant epilepsy). In our series, we did not observe ESES, and the alpha rhythms present in patients < 2y.o during non-REM sleep did not resemble the previously described alpha-delta pattern (Arkilo et al., 2016).

Neither age nor duplication type significantly predicted beta power in the awake state within previous dup15q series (Frohlich et al., 2016; Saravanapandian et al., 2020). Beta power did not significantly differ between patients with and without epilepsy, in contrast to beta peak frequency (BPF), which was lower in children with epilepsy compared to those without epilepsy (Saravanapandian et al., 2020). BPF has previously been described as very stable across repeated longitudinal visits (Saravanapandian et al., 2020), but consecutive EEGs analyzed for each patient were all within a 12 months interval. Conversely, we observed a global modification of BPF, which tended to increase with ageing, switching from beta low (17 Hz) to beta high (27 Hz) in children older than 6y.o. However, not all the patients were represented in every age group. Further exploration of longitudinal EEGs over more extended periods of time is therefore necessary.

In our study population, localization of RR varied with ageing, switching from diffuse localization at an early age to a more anterior predominance, observed upon visual analysis and confirmed by power spectrum analysis after the age of 2y.o. Considering our limited sample size, this observation requires replication in a larger cohort of patients. Nevertheless, such developmental changes in brain activity over the frontal areas has already been reported in the literature (Battaglia et al., 2016). Frohlich et al. had also observed that beta oscillations (in mainly non-epileptic dup15q patients) were diffuse across the scalp with the largest effect size in the fronto-temporal regions. This topography resulted from averaging across channels and participants so that an association between age and topography is difficult to evaluate. However, the anterior predominance in *Frohlich*'s averaged study group could be in line with our observation of the shifting predominance of RR towards anterior regions after the age of 2 years, as the median age of their series was 54 months (Frohlich et al., 2016, 2019). These findings might suggest a possible influence of the posterior to anterior emergence of brain maturation (Chiron et al., 1992). Urraca et al. (Urraca et al., 2013) had noticed that RR tended to disappear at adolescence in dup15q patients. In our series, the eldest age at last EEG follow-up was 12 years (patient C) therefore EEGs of older patients such as adolescents were not analyzed.

Fast beta activity has also been reported in other conditions such as infantile neuroaxonal dystrophy (INAD), particularly in phospholipase-A2 associated neurodegeneration, where RR have been described as either localized or more diffuse (Romani et al., 2015; Gitiaux et al., 2018), of high amplitude after the age of 2 years (Iodice et al., 2017), present in both wakefulness and sleep states with a predominance on anterior leads (Ferriss et al., 1977; Nardocci et al., 1999). Interestingly, in two patients the excessive beta rhythms raised the differential diagnosis of INAD as their epileptic encephalopathy induced psychomotor regression mimicking the clinical course of INAD. Compared to INAD where RR are rarely observed before the age of 2 years, in our series RR were visually present as early as 7 months on available EEGs and diminished significantly in sleep.

Although precise pathophysiology of beta-band RR generation in dup15q remains unknown, a link between beta rhythms in dup15q syndrome and GABA-ergic excessive activity due to copy number gains of the BP2-BP3 region involving $GABA_A$-receptor genes cluster (*GABRB3*, *GABRA5* and *GABRG3*) has been raised in literature (Urraca et al., 2013; Frohlich et al., 2019; Saravanapandian et al., 2020) and mutations within *GABRB3* gene have been directly linked to epileptic encephalopathy (Epi4K Consortium, 2013). This relationship was first suspected due to the similar aspect of EEGs in dup15q patients, compared to the beta rhythms induced by $GABA_A$-modulators such as benzodiazepines and that originate from the primary sensorimotor cortex (Jensen et al., 2005). Beta band rhythms can be of various therapeutic origin among which benzodiazepines (Jensen et al., 2005), barbiturates (Bellville et al., 1956) or Vigabatrin with dose-dependently increased beta-power under Vigabatrin and Diazepam (Bouwman et al., 2004). $GABA_A$-receptor modulation resulting from 15q duplication has recently been suggested (Saravanapandian et al., 2020). Fast rhythms, within beta-gamma ranges, are present in the background electrical activity during the brain-activated states of waking and REM sleep (Steriade et al., 1990; Steriade and Timofeev, 2003). Herein, it is interesting to note that the physiological process of beta rhythms decreasing in non-REM-sleep is respected in epileptic dup15q children, in spite of the duplication of $GABA_A$-receptor genes cluster.

Although the link between beta rhythms in dup15q and GABA-ergic activity due to copy number gain of $GABA_A$-receptor genes cluster seems plausible in light of the indirect indicators discussed above, involvement of other genes associated in the pathogenesis of seizures should also be considered. *UBE3A*, lying within BP2-BP3, encoding a ubiquitin protein ligase, is critical for brain development and synaptic function. It is maternally expressed (paternally imprinted) in most neurons, and functional loss of the UBE3A protein is responsible for the Angelman syndrome, another genetic neurodevelopmental disorder presenting with severe ID and epilepsy. EEGs in most Angelman patients show a typical aspect of diffuse high voltage monomorphous theta-delta slowing in the awake state that could be regarded as an opposite « mirror-EEG-phenotype » to the excessive fast activity in dup15q. However, this beta EEG phenotype in dup15q is not only found in cases of maternal dup15q syndrome but also seen in paternal duplications, in which *UBE3A* is minimally impacted. This suggests a crucial role for the non-imprinted 15q genes, rather than *UBE3A*, in generating fast rhythms in dup15q (Frohlich et al., 2019; Saravanapandian et al., 2020). Besides, *CHRNA7* lying within BP4-BP5, coding for a subunit of the neuronal nicotinic receptor found in some GABA-ergic interneurons has also been associated with epilepsy (Gillentine and Schaaf, 2015). It may contribute to the epilepsy and seizure phenotype in the patients with idic15 involving the region between BP4 and BP5 (Battaglia et al., 2016).

5. Conclusion

In our dup15q study group, WS and LGS were the main epilepsy syndromes observed and occurred mostly in idic15 patients. Focal epilepsy was observed in intdup15 group. Seizure control occurred less frequently in idic15 compared to intdup15 patients. In WS, hypsarrhythmia was most frequently atypical, and a pattern of posterior predominant spike/polyspike bursts could be observed in idic15 patients. We confirmed the previously reported presence of beta-band RR during wakefulness and enlarged the findings that these RR decreased in non-REM sleep and shifted from diffuse to anterior localization with ageing. This electro-clinical aspect may be a recognizable pattern pointing towards dup15q diagnosis in children with autism spectrum disorder and developmental delay.

Author contributions

Patient's recruitment and cytogenetics: V. M., S. R., O. R. Evaluation of subjects: M.-T. D., M. E., A. K., D. C.-Z., C. S., P. V.-D., N. B.-B., C. B., N. C., C. G., M. H., M. B., A. G., M. R., A. M., I. D. Analysis and interpretation of data: M.-T. D., G. D., V. M., A.K., M.E. Revision of the research report: M.E., A.K., R.N.

All authors have approved the final article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.02.010.

References

Al Ageeli E, Drunat S, Delanoë C, Perrin L, Baumann C, Capri Y, et al. Duplication of the 15q11-q13 region: Clinical and genetic study of 30 new cases. Eur J Med Genet 2014;57:5–14. https://doi.org/10.1016/j.ejmg.2013.10.008.

Arkilo D, Devinsky O, Mudigoudar B, Boronat S, Jennesson M, Sassower K, et al. Electroencephalographic patterns during sleep in children with chromosome 15q11.2-13.1 duplications (Dup15q). Epilepsy Behav 2016;57:133–6. https://doi.org/10.1016/j.yebeh.2016.02.010.

Bahi-Buisson N, Ville D, Eisermann M, Plouin P, Kaminska A, Chiron C. L'épilepsie dans les aberrations chromosomiques. Arch Pédiatrie 2005;12:449–58. Available from https://linkinghub.elsevier.com/retrieve/pii/S0929693X04006608.

Battaglia A. The inv dup (15) or idic (15) syndrome (Tetrasomy 15q). Orphanet J Rare Dis 2008;3:30. Available from https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-3-30.

Battaglia A, Bernardini L, Torrente I, Novelli A, Scarselli G. Spectrum of epilepsy and electroencephalogram patterns in idic (15) syndrome. Am J Med Genet Part A 2016;170:2531–9.

Battaglia A, Gurrieri F, Bertini E, Bellacosa A, Pomponi MG, Paravatou-Petsotas M, et al. The inv dup(15) syndrome: A clinically recognizable syndrome with altered behavior, mental retardation, and epilepsy. Neurology 1997;48:1081–6. Available from http://www.neurology.org/cgi/doi/10.1212/WNL.48.4.1081.

Battaglia A, Parrini B, Tancredi R. The behavioral phenotype of the idic(15) syndrome. Am J Med Genet Part C Semin Med Genet 2010;154C:448–55. Available from http://doi.wiley.com/10.1002/ajmg.c.30281.

Bellville JW, Howland WS, Boyan CP. Comparison of the electroencephalographic patterns during steroid and barbiturate narcosis. Br J Anaesth 1956;28:50–4. https://doi.org/10.1093/bja/28.2.50.

Benarroch EE. GABAA receptor heterogeneity, function, and implications for epilepsy. Neurology 2007;68:612–4. Available from http://www.neurology.org/cgi/doi/10.1212/01.wnl.0000255669.83468.dd.

Bolton PF, Dennis NR, Browne CE, Thomas NS, Veltman MWM, Thompson RJ, et al. The phenotypic manifestations of interstitial duplications of proximal 15q with special reference to the autistic spectrum disorders. Am J Med Genet 2001;105:675–85. Available from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=33101466.

Bouwman BM, Heesen E, van Rijn CM. The interaction between vigabatrin and diazepam on the electroencephalogram during active behaviour in rats: an isobolic analysis. Eur J Pharmacol 2004;495:119–28. Available from https://linkinghub.elsevier.com/retrieve/pii/S0014299904005217.

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;15:380–5.

Chifari R, Guerrini R, Pierluigi M, Cavani S, Sgrò V, Elia M, et al. Mild generalized epilepsy and developmental disorder associated with large Inv Dup(15). Epilepsia 2002;43:1096–100. Available from http://doi.wiley.com/10.1046/j.1528-1157.2002.34101.x.

Chiron C, Raynaud C, Mazière B, Zilbovicius M, Laflamme L, Masure MC, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. J Nucl Med 1992;33:696–703. Available from http://www.ncbi.nlm.nih.gov/pubmed/1569478.

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;55:396–402. Available from http://doi.wiley.com/10.1111/epi.12530.

Cook 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;60:928–34. Available from http://www.ncbi.nlm.nih.gov/pubmed/9106540%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1712464.

Dennis NR, Veltman MWM, 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 Part A 2006;140A:434–41. Available from http://doi.wiley.com/10.1002/ajmg.a.31091.

Dittrich B, Buiting K, Korn B, Rickard S, Buxton J, Saitoh S, et al. Imprint switching on human chromosome 15 may involve alternative transcripts of the SNRPN gene. Nat Genet 1996;14:163–70. Available from http://www.nature.com/articles/ng1096-163.

Epi4K Consortium E. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217–21. Available from: http://www.nature.com/articles/nature12439.

Ferriss GS, Happel LT, Duncan MC. Cerebral cortical isolation in infantile neuroaxonal dystrophy. Electroencephalogr Clin Neurophysiol 1977;43:168–82.

Finucane BM, Lusk L, Arkilo D, Chamberlain S, Devinsky O, Dindot S, et al. 15q Duplication Syndrome and Related Disorders Available from:. GeneReviews® 2016.

Frohlich J, Reiter LT, Saravanapandian V, DiStefano C, Huberty S, Hyde C, et al. Mechanisms underlying the EEG biomarker in Dup15q syndrome. Mol Autism 2019;10:29. Available from: https://molecularautism.biomedcentral.com/articles/10.1186/s13229-019-0280-6.

Frohlich J, Senturk D, Saravanapandian V, Golshani P, Reiter LT, Sankar R, et al. A Quantitative Electrophysiological Biomarker of Duplication 15q11.2-q13.1 Syndrome. Ravel N, editor. PLoS One 2016;11:e0167179. Available from: https://dx.plos.org/10.1371/journal.pone.0167179.

Gillentine MA, Schaaf CP. The human clinical phenotypes of altered CHRNA7 copy number. Biochem Pharmacol 2015;97:352–62. Available from https://linkinghub.elsevier.com/retrieve/pii/S0006295215003287.

Gitiaux C, Kaminska A, Boddaert N, Barcia G, Guéden S, The Tich SN, et al. PLA2G6-associated neurodegeneration: Lessons from neurophysiological findings. Eur J Paediatr Neurol 2018;22:854–61. https://doi.org/10.1016/j.ejpn.2018.05.005.

Gramfort A, Luessi M, Larson E, Engemann DA, Strohmeier D, Brodbeck C, et al. MNE software for processing MEG and EEG data. Neuroimage 2014;86:446–60.

Hogart A, Wu D, LaSalle JM, Schanen NC. The comorbidity of autism with the genomic disorders of chromosome 15q11.2-q13. Neurobiol Dis 2010;38:181–91. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf.

Iodice A, Spagnoli C, Salerno GG, Frattini D, Bertani G, Bergonzini P, et al. Infantile neuroaxonal dystrophy and PLA2G6-associated neurodegeneration: An update for the diagnosis. Brain Dev 2017;39:93–100. https://doi.org/10.1016/j.braindev.2016.08.012.

Jas M, Engemann D, Raimondo F, Bekhti Y, Gramfort A. Automated rejection and repair of bad trials in MEG/EEG. PRNI 2016 - 6th International Workshop on Pattern Recognition in Neuroimaging, 2016.

Jensen O, Goel P, Kopell N, Pohja M, Hari R, Ermentrout B. On the human sensorimotor-cortex beta rhythm: Sources and modeling. Neuroimage 2005;26:347–55. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1053811905001060.

Lefebvre A, Delorme R, Delanoë C, Amsellem F, Beggiato A, Germanaud D, et al. Alpha waves as a neuromarker of autism spectrum disorder: the challenge of reproducibility and heterogeneity. Front Neurosci 2018;12:662. Available from https://www.frontiersin.org/article/10.3389/fnins.2018.00662/full.

Matricardi S, Darra F, Spalice A, Basti C, Fontana E, Dalla Bernardina B, et al. Electroclinical findings and long-term outcomes in epileptic patients with inv dup (15). Acta Neurol Scand 2018;137:575–81. Available from http://doi.wiley.com/10.1111/ane.12902.

Mattei MG, Souiah N, Mattei JF. Chromosome 15 anomalies and the Prader-Willi syndrome: Cytogenetic analysis. Hum Genet 1984;66:313–34. Available from http://link.springer.com/10.1007/BF00287636.

Mohandas TK, Park JP, Spellman RA, Filiano JJ, Mamourian AC, Hawk AB, et al. Paternally derived de novo interstitial duplication of proximal 15q in a patient with developmental delay. Am J Med Genet 1999;82:294–300.

Moreno-De-Luca D, Sanders SJ, Willsey AJ, Mulle JG, Lowe JK, Geschwind DH, et al. Using large clinical data sets to infer pathogenicity for rare copy number

variants in autism cohorts. Mol Psychiatry 2013;18:1090–5. https://doi.org/10.1038/mp.2012.138.
Nardocci N, Zorzi G, Farina L, Binelli S, Scaioli W, Ciano C, et al. Infantile neuroaxonal dystrophy: Clinical spectrum and diagnostic criteria. Neurology 1999;52. 1472 1472 Available from http://www.neurology.org/cgi/doi/10.1212/WNL.52.7.1472.
Orrico A, Zollino M, Galli L, Buoni S, Marangi G, Sorrentino V. Late-onset Lennox-Gastaut syndrome in a patient with 15q11.2-q13.1 duplication. Am J Med Genet Part A 2009;149A:1033–5. Available from: http://doi.wiley.com/10.1002/ajmg.a.32785.
Roberts SE, Dennis NR, Browne CE, Willatt L, Woods GC, Cross I, et al. Characterisation of interstitial duplications and triplications of chromosome 15q11–q13. Hum Genet 2002;110:227–34. Available from http://link.springer.com/10.1007/s00439-002-0678-6.
Roberts SE, Maggouta F, Thomas NS, Jacobs PA, Crolla JA. Molecular and fluorescence in situ hybridization characterization of the breakpoints in 46 large supernumerary marker 15 chromosomes reveals an unexpected level of complexity. Am J Hum Genet 2003;73:1061–72.
Rocha J, Guerra C, Oliveira R, Dória S, Rego R, Rosas MJ. Late-onset Lennox-Gastaut syndrome as a phenotype of 15q11.1q13.3 duplication. Epileptic Disord 2012;14:159–62. Available from: http://www.john-libbey-eurotext.fr/medline.md?doi=10.1684/epd.2012.0502.
Romani M, Kraoua I, Micalizzi A, Klaa H, Benrhouma H, Drissi C, et al. Infantile and childhood onset PLA2G6-associated neurodegeneration in a large North African cohort. Eur J Neurol 2015;22:178–86.
Saravanapandian V, Frohlich J, Hipp JF, Hyde C, Scheffler AW, Golshani P, et al. Properties of beta oscillations in Dup15q syndrome. J Neurodev Disord 2020;12:22. Available from https://jneurodevdisorders.biomedcentral.com/articles/10.1186/s11689-020-09326-1.
Stankiewicz P, Lupski JR. Genome architecture, rearrangements and genomic disorders. Trends Genet 2002;18:74–82. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168952502025921.
Steriade M, Gloor P, Llinás RR, Lopes da Silva FH, Mesulam M-M. Basic mechanisms of cerebral rhythmic activities. Electroencephalogr Clin Neurophysiol 1990;76:481–508. Available from: https://linkinghub.elsevier.com/retrieve/pii/001346949090001Z.
Steriade M, Timofeev I. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. Neuron 2003;37:563–76. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0896627303000655.
Urraca N, Cleary J, Brewer V, Pivnick EK, McVicar K, Thibert RL, et al. The Interstitial Duplication 15q11.2-q13 Syndrome Includes Autism, Mild Facial Anomalies and a Characteristic EEG Signature. Autism Res 2013;6:268–79. Available from: http://doi.wiley.com/10.1002/aur.1284.
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;117:803–9. Available from https://linkinghub.elsevier.com/retrieve/pii/S1388245705005237.
Welch PD. The use of fast fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms. IEEE Trans Audio Electroacoust 1967;15:70–3.